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Using CSF biomarkers to understand mechanisms of behavioral changes and effects of drug treatment in dementia

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USING CSF BIOMARKERS TO UNDERSTAND MECHANISMS OF BEHAVIORAL CHANGES AND EFFECTS OF DRUG TREATMENT IN DEMENTIA

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Dedicated to my family, friends and all other loved ones who supported me in times of struggle and motivated me to find my way in life.

ABSTRACT

Dementia is affecting millions of people around the world, and the global prevalence will continuously rise. Neuropsychiatric symptoms (NPS) in dementia are frequent and constitute a key driving force in the disease burden for both patients, families, caregivers and society. The clinical presentation includes symptoms such as agitation, depression, anxiety, apathy and irritability, which are highly frequent in patients with dementia. NPS have a significant negative impact on a patient's ability to perform activities of daily living and also contribute largely to the disease-associated health care costs. Current knowledge of the pathophysiological mechanisms causing NPS is lacking, and improved understanding of these processes is of great importance in order to improve treatment of NPS.

The main purpose of this thesis was to examine the pathophysiological mechanisms underlying NPS by investigating their associations to cerebrospinal fluid (CSF) biomarkers reflecting core Alzheimer's dementia (AD) pathology (phosphorylated-tau [P-tau], total-Tau [T-tau], β-amyloid 1-42 [Aβ-1-42]), synaptic degeneration (neurogranin [Ng], growth-associated protein 43 [GAP-43]) and axonal degeneration (neurofilament light protein [NFL]) in patients with dementia. Secondary aims included investigation of how treatment with an acetylcholinesterase inhibitor (AChEI) (Galantamine) or antipsychotic (Risperidone) impacts both the clinical symptoms and CSF biomarker patterns. In the first study, we showed that agitation correlated with increased levels of P-tau and T-tau in CSF, but not with Aβ-1-42. Thus, suggesting an association between agitation and tau-mediated pathology. The second study was an open randomized clinical trial comparing the efficacy of Galantamine and Risperidone for the treatment of agitation in patients with dementia. Both drugs were effective in reducing levels of agitation. However, Risperidone was more efficient at decreasing NPS, although at the cost of lower tolerability and increased rate of adverse events. In the third study, we showed that treatment with Risperidone, but not Galantamine, was associated with a decrease of CSF Aβ-1-42. Indicating a potential association between Risperidone and progression of amyloid pathology. In the fourth study, we investigated the association between NPS and biomarkers for synaptic degeneration (Ng, GAP-43) and axonal degeneration (NFL). Levels of Ng, GAP-43 and NFL did not differ between AD patients with high vs low levels of NPS. We also found associations between CSF markers for synaptic (Ng, GAP-43) and axonal degeneration (NFL) with NPS, especially of the psychotic spectrum, in patients with vascular dementia (VaD).

In conclusion, our results implicate tau-mediated pathology and synaptic dysfunction as contributing components to the presence of NPS in AD and VaD. In contrast, no clear evidence supporting the role of amyloid pathology in NPS was observed. Interestingly, treatment with Risperidone affected CSF Aβ-1-42 levels, providing a possible pathway for the previously observed association between use of antipsychotics and accelerated rate of cognitively decline seen in patients with dementia.

LIST OF SCIENTIFIC PAPERS

I. **Bloniecki V**, Aarsland D, Cummings J, Blennow K, Freund-Levi Y. Agitation in dementia: relation to core cerebrospinal fluid biomarker levels. Dement Geriatr Cogn Dis Extra. 2014;4(2):335–43

II. Freund-Levi Y, **Bloniecki V**, Auestad B, Tysen Bäckström AC, Lärksäter M, Aarsland D. Galantamine versus Risperidone for Agitation in People with Dementia: A Randomized, Twelve-Week, Single-Center Study. Dement Geriatr Cogn Disord. 2014;38(3–4):234–44

III. **Bloniecki V**, Aarsland D, Blennow K, Cummings J, Falahati F, Winblad B, Freund-Levi Y. Effects of Risperidone and Galantamine Treatment on Alzheimer's Disease Biomarker Levels in Cerebrospinal Fluid. J Alzheimer's Dis. 2017;57(2):387–93

IV. **Bloniecki V**, Zetterberg H, Aarsland D, Vannini P, Kvartsberg H, Winblad B, Blennow K, Freund-Levi Y. Are neuropsychiatric symptoms in dementia linked to CSF biomarkers of synaptic and axonal degeneration?

CONTENTS

LIST OF ABBREVIATIONS

Aβ	Amyloid β
ACC	Anterior cingulate cortex
AChEI	Acetylcholinesterase inhibitor
AD	Alzheimer's disease
ADL	Activities of daily living
AP	Amyloid plaques
APP/*APP*	Amyloid precursor protein (gene)
APOE/*APOE*	Apolipoprotein E (gene)
BACE1	Beta-site amyloid precursor protein cleaving enzyme 1
BBB	Blood brain barrier
BPSD	Behavioral and psychological symptoms of dementia
C-terminal	Carboxyl terminus
CMAI	Cohen Mansfield Agitation Inventory
CNS	Central nervous system
CSF	Cerebrospinal fluid
DLB	Dementia with Lewy bodies
EOAD	Early-onset Alzheimer's disease
FDG	Fluorodeoxyglucose
GABA	Gamma-aminobutyric acid
LB	Lewy bodies
LBD	Lewy bodies disease
LC	Locus coeruleus
LDLR	Light density lipoprotein receptor
LOAD	Late-onset Alzheimer's disease
LRP1	Low-density lipoprotein receptor-related protein 1
FAD	Familial Alzheimer's disease

FDA	Food and Drug administration
FTD	Frontotemporal dementia
FTLD	Frontotemporal lobar degeneration
IDE	Insulin-degrading enzyme
MBI	Mild behavioral impairment
MCI	Mild cognitive impairment
MIX	Mixed dementia
MMSE	Mini Mental State Examination
MND	Major neurocognitive disorder
MoCA	Montreal Cognitive Assessment
MTBR	Microtubule binding region
NCD	Neurocognitive disorder
NEP	Neprilysin
NFT	Neurofibrillary tangles
Ng	Neurogranin
NPI	Neuropsychiatric Inventory
NPS	Neuropsychiatric symptoms
N-terminal	Amino terminus
PCC	Posterior cingulate cortex
PDD	Parkinson’s disease dementia
PET	Positron emission tomography
PIB	Pittsburgh compound B
PSEN	Presenilin
RAGE	Receptor for advanced glycation end products
ROS	Reactive oxygen species
VaD	Vascular dementia
VCI	Vascular Cognitive Impairment

1 INTRODUCTION

Neuropsychiatric symptoms (NPS) in dementia are a prominent and clinically significant feature of neurocognitive disorders. NPS includes a wide array of different behavioral abnormalities, for example, psychotic behaviors or mood disorders, with typical clinical symptoms including depression, anxiety, apathy, agitation or hallucinations (1). Although NPS contributes immensely to the dementia disease burden, previous research has mostly been focused on cognitive impairment and the decline of memory performance associated with dementia.

Currently, our understanding of the mechanisms causing NPS in dementia is limited, although some evidence for the neuropathological alterations associated with the development of NPS have started to emerge. Treatment of NPS is also currently focused solely on symptom management, whereas no disease-modifying drugs are available. Current medications display modest efficacy at best, while these symptoms continue to cause enormous distress for both patients and caregivers (2). There is, therefore, a great need for improved clinical care, as well as a necessity for further basic research, in order to amend the existing knowledge gap regarding NPS neuropathology.

The purpose of this thesis was to study the underlying pathophysiological mechanisms associated with NPS through the analysis of correlations with cerebrospinal fluid (CSF) biomarkers reflecting core Alzheimer's disease (AD) pathology (Total-tau [T-tau], phosphorylated-tau [P-tau], β-amyloid 1-42 [Aβ1-42]), synaptic dysfunction (Neurogranin [Ng], Growth-associated protein 43 [GAP-43]) and axonal degeneration (Neurofilament light protein [NFL]). Secondly, the scope of this thesis was also to investigate the efficacy of drugs currently used against NPS in modern health care (acetylcholinesterase inhibitors and antipsychotics), as well as examine the potential effects of these medications on the CSF biomarker patterns.

Our hope is that this thesis will inspire future research to continue reaching for a more comprehensive understating of the neurobiological and pathological alterations involved in the evolution of NPS. Consequently, providing a basis for the development of new treatment options, thus improving the quality of life for patients, families and caregivers for generations to come.

1.1 Dementia

Dementia, or in updated modern nomenclature, major neurocognitive disorder (NCD) (3) is a universal umbrella term for a clinical syndrome caused by a group of progressive heterogeneous neurodegenerative diseases resulting in deterioration of cognitive functions and a presence of various neuropsychiatric symptom (4).

Earlier global estimates have shown that in 2010, approximately 35.6 million people suffered from dementia. The prevalence is projected to double every two decades, thus anticipating approximately 65.7 million affected patients in 2030 (5). The most common form of dementia worldwide is AD constituting approximately 60-80% of the total prevalence (6). The three other major subtypes of dementia diseases include; Vascular dementia (VaD), Dementia with Lewy bodies (DLB) and Frontotemporal dementia (FTD) with prevalence estimations at approximately 20-40%, 5-20% and 5-20% respectively, depending on the literature cited (4,6). Other less frequent, but still clinically significant, subtypes of dementia include prion-diseases, Huntington's disease, Parkinson's disease dementia, alcohol-related dementia and normal-pressure hydrocephalus (4,7). The single most important risk factor for the development of dementia is age and the prevalence amongst individuals older than 65 is approximately 5-10 % with some variations depending on geographic region (8). Several other factors contribute to the risk of developing dementia including; cardiovascular morbidity, prior head injuries, psychiatric diseases such as depression and genetic factors, most notably, the presence of the ε4 allele variant on the Apolipoprotein E (*APOE*) gene for AD (8–10).

The most characteristic clinical symptom in the majority of dementia cases is a notable decline in memory functions as well as the presence of NPS (4). Other cognitive domains commonly affected include, but are not limited to, deficits in executive functions, learning, language, motor functions and attention (4,8). It is important to note that although all types of dementia result in an overall impairment of cognitive functioning, the clinical phenotype between dementia subtypes may display a large variability depending on the underlying etiologies and associated disease mechanisms (11). Additionally, it is of significance to understand that although different dementia disorders are thought of as distinct neuropathological entities, they often coexist concurrently rather than acting solitarily (12). Indeed, post mortem autopsy studies conducted have confirmed that dementia patients often exhibit mixed pathological alterations including, for example, protein depositions typical for AD as well as vascular morbidity associated with VaD (12,13).

1.1.1 Mild Cognitive Impairment

Mild cognitive impairment (MCI) is a term describing patients with objective impairment in at least one cognitive domain but with preserved independent functionality in daily life, thus not fulfilling the criteria for a dementia diagnosis (14). MCI is thought of as an early stage in the dementia disease continuum and often associated with AD, but can be caused by different underlying pathologies (15).

The prevalence of MCI is roughly 10-20 % in populations older than 65 years of age and more frequent in males as compared to females, but females with MCI show an accelerated rate of cognitive decline as compared to males (16,17).

Patients with MCI have an increased risk of developing dementia, and the annual conversation rate is approximately 5-20 % per year with 80% of patients progressing to dementia within six years after the initial MCI diagnosis (16,18). The symptomatology of MCI syndrome is highly heterogeneous, generating historical difficulties in establishing adequate diagnostic criteria. Current guidelines divide MCI into subtypes depending on the presence of memory deficits referred to as amnestic-MCI and non-amnestic MCI (19). Additionally, whether one or more cognitive domain(s) are impaired is assessed and denoted as single domain MCI or multiple domain MCI, thus creating four potential subtypes when combining these parameters (19).

Of interest, not all patients with neurobiological evidence of preclinical AD, i.e. CSF biomarker patterns suggesting AD pathology or even manifest MCI, progress on the disease continuum and develop AD or other dementias, despite sharing similar cerebral pathological alterations (16,20,21). Predicting which patient will progress from MCI to manifest dementia on an individual level is currently impossible, and the reasons for the variability in disease evolution amongst patients are not fully understood. Albeit, factors such as *APOE* genotype and cardiovascular co-morbidity are considered to be of importance (20,22).

1.1.2 Alzheimer's disease

The term Alzheimer's disease was first introduced in the early 19th century when Dr. Alois Alzheimer, a German psychiatrist and neuropathologist, presented a case study on a relatively young woman suffering from inexplicable progressive memory loss, disorientation and hallucinations which led to eventual death. Subsequent post mortem autopsy studies of her brain conducted by Dr. Alzheimer revealed cerebral atrophy and protein depositions representing the classical neuropathological manifestations of AD (23,24).

There are two main forms of AD; sporadic or familial AD (FAD). Sporadic AD can be further subdivided into late-onset AD (LOAD) and early-onset AD (EOAD). LOAD is the overwhelmingly most common form of AD, constituting more than 95% of all cases, with disease onset over the age of 65 and a mean age of onset at 80 years of age (25). EOAD manifests before 65 years of age and is associated with a more aggressive clinical course, constituting approximately 5% of all AD cases (25–28). FAD is a rare inherited form of the disease, representing less than 1% of all AD cases (25). FAD is most frequently caused by mutations in one of three genes; Amyloid precursor protein (*APP*), presenilin 1 (*PSEN1*) and presenilin 2 (*PSEN2*) inherited in autosomal dominant fashion. Consequently, offspring to patients carrying these mutations have a 50% chance of acquiring the disease (29).

From a clinical perspective, the quintessential feature of AD is progressive memory loss in combination with variable decline in other cognitive domains, often affecting learning capabilities, verbal skills, executive functions and visuospatial abilities, simultaneously accompanied by the presence of various NPS (30,31). Since AD is a chronic progressive disease existing on a continuous temporal spectrum, the clinical symptomatology is highly variable and fluctuates depending on the current disease stage of the individual patient (30). Long before memory loss or other cognitive deficits can be observed, AD-associated pathological changes can be identified in the brain through measurement of CSF biomarkers or imagining technique's, a stage called preclinical AD (21). Patients with preclinical AD can progress and develop cognitive impairment, most frequently involving subtle changes in memory capabilities, that are objectively verifiable through clinical testing using screening instruments such as the Montreal Cognitive Assessment (MoCA) or Mini Mental State Examination (MMSE) (32–34). If this progression occurs, an MCI diagnosis can be established, the next stage on the AD disease continuum (14,21). Although patients with MCI display manifest cognitive impairment, it has per definition of the diagnostic criteria, minor to no impact on their ability to adequately perform activities of daily living (ADL) (14).

Some patients with MCI will experience progression of their symptoms causing a significant negative impact on their ability to independently conduct activities of daily life, thus fulfilling the clinical criteria for a diagnosis of dementia or major NCD according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) (35). Additionally, further diagnostic procedures include assessment of clinical profiles, blood samples to exclude other diseases, brain imaging as well as analysis of CSF biomarkers in order to generate evidence to support the final diagnosis of AD or other dementia subtypes (36). When a diagnosis has been established the clinical projection of AD can broadly be divided into a spectrum consisting of three main stages based on the development and presentation of symptoms namely; mild, moderate and severe AD (37). The variability in symptoms and disease burden between these stages is of great significance, as is the intrapersonal perception of the disease. Mild AD has lower, yet significant, impact on cognitive capabilities and the ability to live a normal life whereas patients who progressed to severe AD display both a major deterioration of general cognitive capabilities and debilitating NPS (30). At this stage of the disease patients are unable to perform almost any ADL functions, consequently leading to institutionalization or constant care and supervision provided by their family members (30,38–40).

Due to the earlier research of Dr. Alzheimer and others, we can today with high accuracy describe the core neuropathological hallmarks of AD. Typical features include cerebral protein deposition causing amyloid plaques (AP) and neurofibrillary

tangles (NFT) with associated synaptic loss and dysfunction, ultimately resulting in neuronal death, gliosis and brain atrophy, most commonly starting in the frontal and temporal lobes and progressively extending to other parts of the neocortex (23,25,41). Although these core pathological alterations have been known for a relatively long time, their specific contribution and temporal relation to the pathogenesis of AD is to this date not completely understood (42). The majority of the scientific community tend to agree with the "amyloid cascade hypothesis", suggesting that amyloid pathology is the driving component in AD development and that NFT constitute a downstream process, but this linear model of disease causality is still debated (25,42,43).

1.1.3 Alzheimer´s pathology – Amyloid plaques

The first pathological hallmark of AD are protein depositions consisting of aggregated β-amyloid (Aβ) located to the extracellular space and walls of blood vessels in the brain denoted amyloid plaques (25,44). The formation of amyloid plaques starts in the frontal and temporal lobe, eventually spreading to the rest of the cerebral cortex as the disease progresses (25,44). Amyloid β (Aβ) denotes a group of peptides with different isoforms ranging between 37 to 43 amino acids in length and exists in two main forms, Aβ1-42 and Aβ1-40, constituted of 42 and 40 residues respectively (45). The Aβ peptide is formed by cleavage of its precursor, amyloid precursor protein (APP), a transmembrane protein genetically located on chromosome 21 thought to be involved in several key biological functions including survival, repair and growth of neurons (44–46).

The metabolism of APP involves cleavage by the different proteases denoted α-, β- and γ-secretases (47). The α-secretases include several enzymes belonging to a class of proteins called a disintegrin and metalloproteinase (ADAM), β-secretases include beta-site APP cleaving enzyme 1 (BACE1) whereas the γ-secretase is a multiprotein complex generated by four different subunits including presenilin 1 or 2, presenilin enhancer 2, nicastrin and anterior pharynx defective 1 (48). The first step involves cleavage of APP by α-or β-secretase into one of two pathways; the amyloidogenic or nonamyloidogenic (45) (Figure 1). In the nonamyloidogenic pathway APP is processed by α-secretases, resulting in soluble APPα and an 83 amino acid long C-terminal part (C83) which is then further processed by γ secretase generating the P3 peptide and APP intracellular domain (AICD) (45).

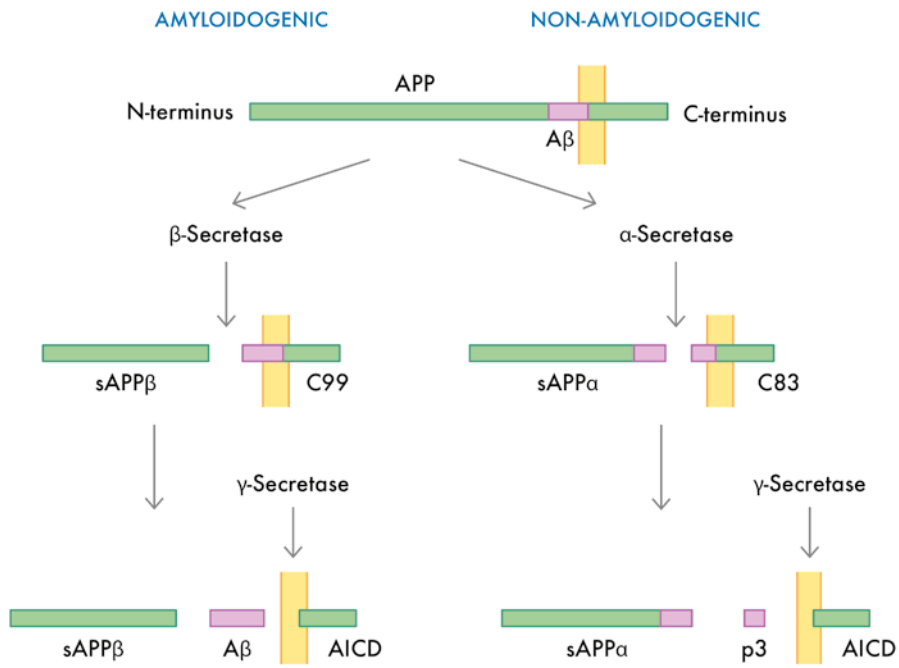

Figure 1. Amyloidogenic and nonamyloid pathways of Aβ metabolism

In the amyloidogenic pathway, modulation of APP by β-secretase (BACE1) generates soluble APPβ and a 99 amino acid long fragment termed (C99) (48). This fragment is then further cleaved by γ secretase to several different isoforms of Aβ resulting in the formation of two main Aβ isoforms, namely Aβ1-40 and Aβ1-42, constituting approximately 60% and 15% of all Aβ peptides when measured in CSF (45,47,49). Currently, the normal physiological function of Aβ peptides remain elusive, but Aβ has been proposed to be involved in the modulation of synaptic activity, plasticity, neuronal survival and memory (50,51). The two main isoforms of Aβ display some differences in functional properties. Most importantly, the 42 amino acid long version is more prone to form oligomers and fibrils, a prerequisite for the generation of amyloid plaques (49). Although Aβ1-40 is the most prevalent Aβ peptide under normal conditions, Aβ1-42 constitutes the main building block of amyloid depositions during AD pathogenesis (49). After Aβ monomers are produced intracellularly, they form oligomers that enter the extracellular space, a step that is currently poorly understood, where they can further organize into protofibrils, which intertwine and develop into mature fibrils in a β-sheet rich configuration, the foundation of amyloid plaques (25,44,45).

Soluble oligomers of Aβ42, more so than mature amyloid plaques, are thought to be responsible for the neurotoxic effects on neurons and synapses, triggering several

pathological events eventually leading to neuronal death and the development of AD (25,52). In early stages of AD, Aβ toxicity seems to have an affinity for cholinergic and noradrenergic neurons located in the nucleus basalis of Meynert and locus coeruleus (LC) respectively, but serotonergic, dopaminergic and glutamatergic neurotransmission is also affected as the disease progresses (53–58). The toxic effects of Aβ pathology are mediated through multiple different mechanisms, and the Aβ oligomers are thought to be the most toxic species in the Aβ family. They can induce oxidative stress by creating free radicals, such as reactive oxidative species (ROS), which directly initiate apoptosis through interaction with cell surface receptors and activate microglia and astrocyte's that induce both direct phagocytosis of neurons and an inflammatory cascade causing damage to neurons (59,60). Aβ can also affect the mitochondria by increased formation of ROS resulting in fragmentation of the organelle, while APP aggregates at the mitochondrial membrane and alters the electron transport chain resulting in mitochondrial dysfunction and increased Aβ production (59). The amyloid plaques cause direct toxicity in their immediate proximity by affecting neurites and causing synaptic dysfunction, but their role as a regional reserve pool of soluble Aβ oligomers is probably more important than their direct neurotoxic effect (61). Furthermore, there is evidence suggesting that Aβ oligomers and monomers, through inflammatory processes or modulation of cellular kinase/phosphatase activity, generate hyperphosphorylation of tau and the formation of neurofibrillary tangles (62). Thus proposing a pathway for β-amyloid as the driving factor of AD-associated neurodegeneration which is the basis for amyloid cascade hypothesis (25,45,59,60)

The catabolism and clearance of Aβ from the brain have been extensively studied since the concentration of cerebral Aβ depends on the equilibrium between formation and degradation of Aβ and impaired clearance could hypothetically be the genesis of AD (48). In fact, there is growing evidence that deceased degradation and clearance of Aβ is the major contributor to late-onset AD whereas the production rates of Aβ are more or less unaffected in this patient group (63,64).

There are three fundamental ways of clearing Aβ peptides from the brain; transport of Aβ over the blood brain barrier (BBB), extracellular proteolytic degradation or receptor-mediated endocytosis by glial cells or macrophages (10,65). Clearance via transportation of Aβ peptides from the central nervous system (CNS) is accomplished through two main processes; either directly into the systemic blood circulation via passage through transport proteins over the BBB or drainage into CSF from where it continues into the blood circulation or lymphatic system (66). Efflux of Aβ peptides directly over the BBB is the primary way of clearance via transportation and is mediated by several membrane receptors, but two are of particular importance, the low-density lipoprotein receptor-related protein 1 (LRP1) and ATP dependent P-glycoprotein 1, whereas the influx of Aβ is regulated by

receptor for advanced glycation end products (RAGE) (41). In AD, the expression of both LRP1 and P-glycoprotein receptors are downregulated, whereas expression of the influx transporter RAGE is increased (66). Simultaneously, oxidative stress caused by the disease process decreases the affinity of Aβ binding proteins in the blood circulation, thus permitting more influx of Aβ through RAGE (66).

Proteolytic degradation of Aβ peptides is an extracellular process in which predominantly different glial cells, such as astrocytes or microglia, produce and secrete different proteases which can cleave Aβ at various sites of the peptide (65,67). The most important enzymes involved in this process include; neprilysin (NEP), insulin-degrading enzyme (IDE), matrix metalloproteinases (MMPs), endothelin-converting enzyme (ECE), plasmin and angiotensin-converting enzyme (ACE) (67). The exact role and importance of the mediators of proteolytic degradation are yet to be determined, but NEP and IDE seem to play a crucial role in Aβ homeostasis (48). Transgenic mice with increased levels of these enzymes show reduced Aβ burden and no formation of amyloid plaques (68), while the decreased activity of both NEP and IDE has been shown in AD patients as compared to healthy controls (69,70) The third way of Aβ clearance involves internalization and degradation of Aβ compounds into the intracellular environment of astrocytes, microglia and macrophages. This predominantly occurs through receptor-mediated endocytosis of fibrillary and oligomeric Aβ, but phagocytosis and pinocytosis also occur, albeit at a lower rate (65). Several different receptors are involved in endocytosis of Aβ peptides, including the LRP1 and RAGE but also scavenger receptors and toll-like receptors (65). Once endocytosis is completed the cell proceeds to degrade the internalized proteins using the ubiquitin-proteasome system or lysosomal processing, both of which can be pathologically altered during AD reducing the clearance capabilities of Aβ (66,67).

Our understating of Aβ metabolism, its relation to amyloid plaques, as well as the identification of mutations associated with familial AD that result in the cerebral accumulation of Aβ (*APP*, *PSEN1* and *PSEN2*) constitutes the basis for the postulation of the amyloid cascade hypothesis (71). The hypothesis suggests that Aβ driven pathology is the upstream event to all neuropathological changes found in AD. The majority of all FAD patients have mutations in one of these three genes, resulting in an overproduction of Aβ1-42 and increased ratios between Aβ1-42 and Aβ1-40 (25,29,72). Furthermore, studies of different transgenic mice models with mutations in FAD associated genes develop clinical and neuropathological features typical of AD, including amyloid plaques, synaptic loss, dystrophic neurites and gliosis (73). Patients with Downs syndrome, who are born with three copies of chromosome 21 containing the *APP* gene, display neuropathological changes close to those in AD 30 years earlier than healthy controls (74,75).

1.1.4 Alzheimer's pathology – Neurofibrillary Tangles

The second classical hallmark of AD neuropathology is the intracellular formation of neurofibrillary tangles in axons, dendrites and soma of neurons (76). The main component of NFTs is tau, a microtubule-associated protein (MAP) found almost exclusively in neurons and genetically coded on the *MAPT* gene located on chromosome 17 (77). Tau exists in 6 different isoforms, ranging in length between 352 to 441 amino acids, with a tubulin-binding domain at the C-terminal and a projection domain at the N-terminal which interacts with cellular proteins, membranes and organelles such as mitochondria (77). The isoforms differ in the C-terminal by having either 3 or 4 microtubule binding region (MTBR) repeats, referred to as R3 or R4, and in the N-terminal by having up to two additional amino acid sequence inserts (77). Although they have principally the same functionality, they likely display specific physiological roles, supported by the fact that expression of the different isoforms is variable depending on the developmental stage (77,78).

The elementary function of tau is to act a stabilizer of microtubules in neuronal axons (78). Tau binding stimulates polymerization of microtubules, and the protein is also a critical component of the axonal transport machinery (77–79). The projection domain of tau regulates the distance between microtubules in axons. It binds to proteins, including spectrin and actin filaments, which enables a connection with neurofilaments and microfilaments, thus playing a pivotal role in the regulation of the cellular cytoskeleton and neuronal morphology (77–79). Under physiological conditions, the modulation of tau binding to microtubules is achieved through several different posttranslational modifications. The most important mechanism involves phosphorylation or dephosphorylation of tau, at one of the approximately 80 serine and threonine residues by intracellular kinases and phosphatases (78,80). This is a dynamic process under careful equilibrium, constantly causing tau to bind and release from microtubules, depending on the phosphorylation state of tau, where increased phosphorylation results in decreased binding affinity (78–80).

Under pathological conditions, such as during AD development, tau disengages from the microtubules resulting in translocation of tau from the axon to the somatodendritic compartment, causing higher concentrations of unbound tau in the cytosol (78,81). Consequently, the monomeric tau protein undergoes dimerization forming tau-dimers which then start to self-assemble into oligomers, which can further elongate and aggregate to generate paired-helical filaments (PHF) and straight filaments, the building blocks of neurofibrillary tangles seen in AD (80,82,83) (Figure 2).

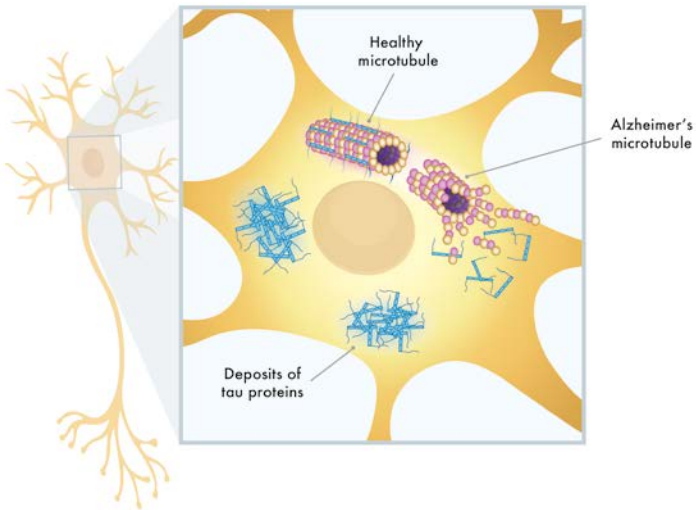

Figure 2. Tau-associated AD pathology

Several hypotheses have been proposed for the pathological alterations required in creating the adequate conditions for the abnormal disengagement of tau from microtubules, and subsequent misfolding and self-aggregation into NFTs. It seems evident that several post-translational mechanisms, including hyperphosphorylation, truncation, acetylation, nitration, glycosylation, ubiquitination and glycation are needed to change the conformational state of tau. These protein alterations promote detachment of tau from microtubules and polymerization into dimers, oligomers, PHFs and finally neurofibrillary tangles (80,82,84). Of these different post-translational mechanisms, hyperphosphorylation of tau seems to be of most importance to engineer the right conditions for tau pathology. Although, but the exact significance and temporal distribution of these factors remain to be established (80). Under physiological conditions, tau is a highly soluble protein and does not aggregate spontaneously as Aβ1-42 (85). The MTBR repeats in tau display β-structure and are prone to self-assembly, but this is usually inhibited by the intact N- and C-terminals which block these regions from interacting and aggregating (79,83).

Post-translational hyperphosphorylation of tau is thought to be one of the earliest and most essential steps in the pathology associated with AD, caused by dysregulation of the balance between kinases and phosphatases (84). Several kinases are upregulated in AD, including Glycogen synthase kinase 3β and Cyclin-dependent protein kinase-5, whereas the activity of protein phosphatase 2A is reduced (80,84). In total, the phosphorylation state of tau is approximately four times higher in AD patients as compared to healthy subjects (80,84). This has several effects on tau, including a decreased affinity for binding to microtubules, stimulates the relocation of tau to the somatodendritic compartments and generates conformational

changes exposing the MTBR regions, prone to aggregation consequently promoting polymerization (79,84). Of interest, AICD transgenic mice show an increased level of tau phosphorylation and neurodegeneration independent of Aβ, suggesting a possible link between tau and Aβ pathology (86).

A second important step in the formation of NFTs is the truncation, or proteolytic cleavage of tau, into smaller parts more prone to aggregation. Several cleavage sites have been identified, but activation of Caspase 3 and subsequent truncation at aspartic acid residue 421, has been shown to promote protein aggregation in vitro (87). Overall, truncation seems to be a crucial step in the promotion of tau-pathology, with these smaller fragments displaying increased aggregation into PHFs and eventually mature tangles (82). Through a complex series of modifications including phosphorylation, truncations and other post-translational mechanisms the tau-protein obtains the properties necessary for agglomeration into higher-order structures such as PHFs, straight filaments and eventually intracellular neurofibrillary tangles.

There are two principal pathways in which tau-mediated neurodegeneration is thought to occur. Firstly, the loss of normal physiological function of tau results in a wide array of pathological events in neurons (88). The detachment of tau from microtubules causes disturbances in the structural and regulatory role of the cytoskeleton and impaired axonal transport, eventually resulting in neuronal dysfunction and cell death (79,84,88). Additionally, translocation of tau from axons and misallocation in dendritic spines results in synaptic dysfunction (89). The second way includes direct toxicity from NFTs and its intermediates. NFTs were long thought to be the primary toxic form of AD-associated neurodegeneration, due to the fact that cognitive impairment is better correlated with the amount of NFTs as compared to amyloid plaques (90). Mature tangles and large fibrils may contribute to neurodegeneration via molecular crowding and neurons with NFTs display fewer synapses (84). However, recent research has shown that the presence of NFTs is not mandatory for neuronal dysfunction, nor does it inhibit local neuronal circuits (91). Instead, small soluble intermediates, such as the oligomers, constitute the primary form of toxic tau species causing neuronal loss and synaptic dysfunction (92,93). Levels of tau oligomers are correlated with clinical symptoms in AD and are tentatively suspected of inducing neurodegeneration via mitochondrial dysfunction while spreading between neurons using prion-like mechanisms (92).

The spatial and temporal distribution of NFTs in AD has long been established to start in the entorhinal cortex, later progressing to the hippocampus and eventually large parts of the neocortex, classically described by Braak staging (I-VI) (81,94) (Figure 3). Recently, the presence of hyperphosphorylated tau in noradrenergic neurons in LC has been suggested as the first pathological change observed in AD (95). These changes are often evident when patients are in their mid-twenties, thus implicating tau as the driving component in AD pathology (95).

1.1.5 Alzheimer's genetics – *APOE*

Genetics is an important risk factor for developing AD (96). Previous studies on twins have indicated that hereditability is a significant contributor to sporadic AD, with more than 60 % of the variation in clinical phenotype attributed to genetic factors (97). FAD is known to be caused by various mutations in specific genes coding for the APP, presenilin-1 and presenilin-2 proteins, explaining approximately 50% of all cases (96). Thus, also implying the existence of other relevant genetic mutations contributing to FAD, which we are currently not aware of (96).

Unlike FAD, sporadic AD is not caused by deterministic inherited mutations, but rather by a combination of environmental factors and multiple genetic risk factors, so-called susceptibility genes (29). The most known and studied susceptibility gene to this date is the one coding for the ε4 allele of Apolipoprotein E (*APOE*). Apolipoprotein E (APOE) is a 299 amino acid long protein involved in lipid homeostasis with its genetic information stored on chromosome 19 (98). Three polymorphic alleles on the *APOE* gene, denoted ε2 (*APOE-ε2*), ε3 (*APOE-ε3*) and ε4 (*APOE-ε4*), encode the three most common isoforms of the protein (APOE2, APOE3, APOE4), with a global prevalence of 8.4%, 77.9% and 13.7% respectively (10). The isoforms diverge at most by two amino acids at position 112 and 158, generating APOE2 (Cys112, Cys158), APOE3 (Cys112, Arg158), and APOE4 (Arg112, Arg158), but this small variation in the amino acid sequence has profound effects on the lifetime risk of developing AD (99).

APOE genotype polymorphism is the single most significant genetic risk factor known in the development of sporadic AD. Carriers on the ε4 allele present an increased probability of disease development, whereas the presence of the ε2 allele is a protective factor (100). The ε4 allele is greatly overrepresented in AD, with approximately 40% of patients showing this genetic variation, as compared to roughly 14 % in the general population (10). Heterozygous carriers of the ε4 allele have a threefold increase in the risk of acquiring AD, while homozygous carriers display a staggering 12-fold increase in the risk of disease development, as compared to non-carriers (25). Additionally, carriers of *APOE-ε4* develop AD at a younger age, with heterozygotes being diagnosed on average 2-5 years earlier, and homozygotes 5-10 years earlier as compared to non-carriers (99). In contrast, carriers of the ε2 allele show decreased risk of developing AD, and if diagnosed display milder cerebral pathology as well as less cognitive impairment (99,101). In total, *APOE* genotype is thought to explain up to 50 % of all late-onset AD cases (102).

APOE is in the CNS mainly produced by astrocytes and functionally contains two domains, the N-terminal receptor-binding domain and the C-terminal lipid-binding domain. It functions as a transporting protein, involved in the transfer of lipids between neurons and over the cellular membrane (98). APOE attaches to

high-density lipoproteins in the CNS and promotes receptor-mediated endocytosis of cholesterol by binding to cell-surface APOE receptors, belonging to the low-density lipoprotein receptor (LDLR) family which includes the LRP1-receptor (10,99). The small changes in amino acid sequence between the three isoforms produce large physiological effects by changing the structure, stability and affinity for binding to APOE receptors as well as different lipids (25,98). APOE2 displays 50-100 times lower binding affinity for the LDRL as compared to APOE3 or APOE4, while APOE4 has been shown to be less stable than APOE3 (98,99).

Several hypotheses have been postulated for how *APOE* affects the pathological processes associated with AD, mostly focusing on amyloid driven pathology, but Aβ independent pathways have also been proposed. Several studies, both human and animal, have shown that *APOE* genotype is associated with levels of Aβ and amyloid plaques in an isoform dependent manner, with ε4 carriers displaying the highest Aβ concentrations (10,25,103). In the CNS, APOE can bind soluble Aβ and promote cellular uptake via receptors, such as the LRP1, at an isoform dependent rate, with APOE4 showing the lowest affinity for Aβ (10). Furthermore, *APOE* genotype has been suggested to affect the clearance rate of Aβ over the BBB and effectiveness of intracellular proteolytic degradation of Aβ (10). The exact role of APOE in AD pathology is not currently established. However, the lipoprotein is thought to contribute by acting as a chaperon protein for Aβ, affecting the clearance rate and the amount of Aβ depositions (25). Some Aβ independent pathways mechanisms for *APOE* in AD pathology have been proposed. These include potential genotype-dependent hyperphosphorylation of tau, regulation of neuroinflammation and mitochondrial dysfunction, but the exact role of *APOE* in these mechanisms remain to be established (98,99).

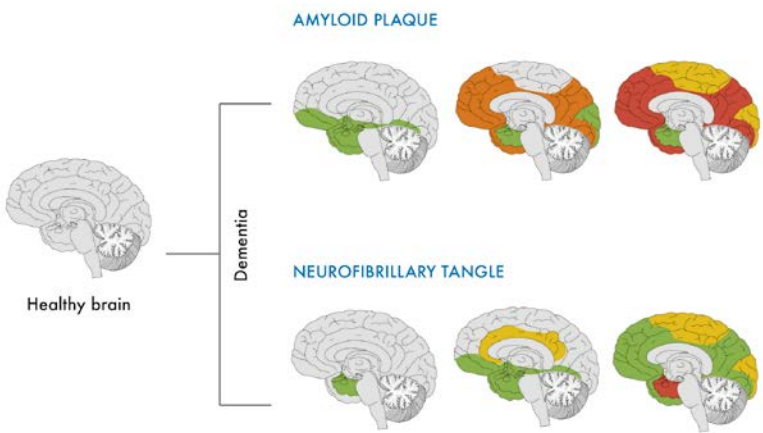

Figure 3. Spatial distribution of APs and NFTs during AD progression

1.1.6 Vascular dementia

Vascular dementia (VaD) is the second most common subtype of dementia, constituting approximately 20% of all dementia cases, and cerebrovascular morbidity is a major risk factor for developing dementia (6,104,105). About 20% of all patients surviving a stroke will develop dementia in their lifetime (106). In modern literature, the term vascular cognitive impairment (VCI), has been introduced to describe the full spectrum of clinical phenotypes from vascular-MCI to VaD (104,105). The term VCI encompasses a heterogeneous group of vascular disorders, with distinct cerebrovascular pathology, contributing to the development of dementia or cognitive impairment, and are broadly defined as a loss of cognitive function due to ischemic or hemorrhagic infarctions and subsequent brain dysfunction (107).

The vascular abnormalities in VCI can broadly be divided into the disease of large or small cerebral vessels, and VaD can further be subdivided into three main subtypes based on the predominant underlying vascular neuropathology; Multi-infarct dementia (cortical vascular dementia), small vessel dementia (subcortical vascular dementia) and strategic infarct dementia. (104,108). The vascular changes causing these subtypes are heterogeneous and different types of vascular abnormalities often coexist simultaneously (104).

The most prevalent subtype of VCI is multi-infarct dementia, caused by cerebrovascular disease of predominantly large vessels with arteriosclerosis and subsequent thromboembolic events. These events cause multiple cortical infarcts of various size and often affect the cingulate and temporal neocortex (105,109). Strategic infarct dementia is also associated with large vessel pathology, but in contrast to multi-infarct dementia only affects specific brain regions involved in cognition such as thalamus or hippocampus due to single infarcts (105). Small vessel dementia is characterized by lacunar infarcts affecting subcortical brain regions as well as cortical and subcortical microinfarcts (110). These pathological changes arise due to underlying hypertension and arteriosclerosis, resulting in diffuse white matter lesions showing demyelination, axonal loss and gliosis, which eventually results in cognitive impairment (110).

From a clinical perspective, VCI/VaD is characterized by three key concepts; cognitive decline, confirmation of vascular pathology by imaging modalities, and in the case of strategic or multi-infarct dementia presence of a temporal relationship between onset of cognitive impairment and vascular disease (111). In contrast to AD, the clinical presentation of VaD is more diverse, and memory is not always the cognitive domain presenting the most severe deterioration (104). The broad spectrum of clinical manifestations in VCI is caused by the spatial specificity of the underlying pathology. Since cerebral damage is often more focal then global, the affected brain region will determine the clinical presentation, and because subcortical regions are often involved patients display more impairments in executive function, attention and information processing (104).

1.1.7 Frontotemporal dementia

Frontotemporal dementia (FTD) is used as an umbrella term describing a heterogeneous group of clinical syndromes, with divergent symptomatology and underlying pathophysiology. These syndromes are united by the presence of focal neurodegeneration located to the prefrontal and anterior temporal neocortex (112). Clinically, it is predominantly characterized by deterioration of executive functioning, behavioral changes and language impairment, often affecting patients under the age of 65 (113). FTD is divided into two main categories depending on clinical presentation; behavioral variant FTD and language variant FTD (114). Behavioral FTD accounts for approximately 50% of all cases and features symptoms such as progressive personality changes, deterioration in social functioning, apathy or disinhibition, which are often misdiagnosed as a psychiatric illness at early stages of the disease (115). The language variant of FTD, also known as primary progressive aphasia, can further be subdivided into non-fluent or semantic variants (113). The non-fluent version present with impairment in speech production or grammar, whereas the semantic variant displays decreased semantic knowledge and word comprehension (113,116)

The pathology of FTD is extremely heterogeneous and complex. Roughly 10% of the disease cases are deterministically hereditary, in an autosomal dominant manner, often caused by mutations in the MAPT gene (113). The predominant neuropathological features of frontotemporal lobar degeneration (FTLD) include gliosis, neuronal loss and microvacuolation in the frontal and temporal lobes that are caused by different protein depositions in the brain (112). Three main histological subgroups can be found classified depending on which protein is accumulated in the brain: FTLD-tau, FTLD-TDP and FTLD-FUS (117). FTLD-tau constitutes approximately 40% of all cases and is caused by the accumulation of tau protein. The typical pathological finding in FTLD-tau is the presence of ballooned neurons, referred to as Pick's cell (115). In the rest of FTD patient's tau pathology is nonexistent. Instead, approximately 50% of cases are caused by the accumulation of TAR DNA-binding protein 43 (FTLD-TDP), and the majority of the remaining cases are associated with aggregation of the fused in sarcoma protein (FTLD-FUS) (113).

1.1.8 Lewy body diseases

Lewy body disease (LBD) is an umbrella term for diseases caused by α-synuclein pathology, including both Parkinson's disease dementia (PDD) and dementia with Lewy bodies (DLB) (118). Although Parkinson's disease is primarily considered a motor disorder, the presence of dementia is common, with patients showing a risk of developing dementia up to six times as high when compared to healthy elderly individuals (119). The pathological hallmark of LBD is the

presence of intraneuronal protein depositions composed of α-synuclein, referred to as Lewy bodies (LB), often localized to structures in the cortex, brainstem and limbic area. LBD results in the loss of predominantly dopaminergic neurons, but also affect cholinergic and noradrenergic neurotransmission (118,120). Similar to tau pathology, the smaller intermediates of Lewy bodies such as α-synuclein oligomers or fibrils, are thought to be the main neurotoxic component in the disease process (118). In contrast, mature LBs have been suggested to have a neuroprotective effect (118,120). The oligomers or fibrils of α-synuclein are thought to alter cell membrane permeability, cause histone dysfunction and inhibit the function of neuronal survival factors, thus resulting in neurodegeneration (120). The spatial distribution of LB constitutes an important difference between PDD and DLB. In DLB, the protein inclusions are diffusely located to large areas of the cerebral cortex. In contrast, LBs in PDD display a more specific pattern affecting predominantly dopaminergic neurons in the substantia nigra, thus resulting in the parkinsonian symptoms seen in PDD (121). DLB also frequently coexist with simultaneous AD pathology, and patients diagnosed with AD are often found to have LB associated pathology at autopsy (122).

The core clinical features of DLB include fluctuating cognitive impairment, visual hallucinations, and physical symptoms relating to parkinsonism (122). The typical fluctuations in cognitive performance are characteristic of DLB and present clinical similarities to delirium (122). Presence of visual hallucinations is also characteristic and experienced in approximately 80% of all cases, which may help to discriminate DLB from other dementias (122). The clinical profile of PDD is similar to DLB, but with less visual hallucinations and more motor symptoms, and patients typically present with less memory dysfunction as compared to AD (118,123). One key clinical difference is the temporal association between the onset of dementia and motor symptoms. In PDD, parkinsonism develops at least one year before the debut of cognitive symptoms, whereas motor symptoms commonly start after cognitive impairment in DLB. (122,124).

1.1.9 Mixed dementia

Different dementia disorders are conceptually thought of as distinct entities with specific and exclusive neuropathology, existing independently of each other. However, several postmortem autopsy studies on dementia patients have shown that various pathological changes often overlap and exist simultaneously (12,13,125). For example, pathology consistent with AD often coexist with cerebral vascular disease associated with VaD, then referred to as mixed type dementia (MIX) (126).

The prevalence numbers for MIX are quite diverging between different studies indicating that between 10-74% of patients display MIX type pathology, and the largest study to this date indicates that MIX is present in more

than 50% of all dementia patients (12). Recently, a review of prior studies focused on the co-occurrence of AD and VaD found that 22% of patients displayed pathological findings associated with both diseases (127). Although the frequent existence of multiple types of neuropathological changes in dementia patients is evident, the specific contribution and interaction between these disease processes remain to be discovered (126,128). Of interest, previous studies have shown that multiple pathologies increases the risk of developing dementia, and is associated with the severity of the disease, suggesting potential synergistic effects between the underlying disease mechanisms (12,129).

1.2 Neuropsychiatric symptoms in dementia

Although memory loss is the primary feature associated with AD in the eye of the general public, many different behavioral and psychiatric disturbances are central features of AD and other dementia diseases (130). These non-cognitive symptoms include, for example, depression, apathy, agitation, disinhibition or psychosis and are in modern literature most commonly referred to as neuropsychiatric symptoms (NPS) in dementia. Albeit, the term behavioral and psychological symptoms in dementia (BPSD) can be used interchangeably (131).

NPS encompasses a wide array of heterogeneous symptoms, ranging from anxiety to delusions, and previous research has tried to factor NPS into larger clusters of clinically related symptoms. Albeit this research is somewhat inconsistent, many studies have described three main clusters consisting of behavioral dysfunction, mood disorders and psychosis. However, other classifications have been proposed, and the terminology used to describe these clusters differ between studies (1,131,132). The behavioral cluster includes symptoms such as agitation/aggression, aberrant motor behavior, disinhibition and irritability. Mood disturbances incorporate, for example, depression, apathy or anxiety, while the psychosis cluster primarily describe delusions and hallucinations (1) (Figure 4).

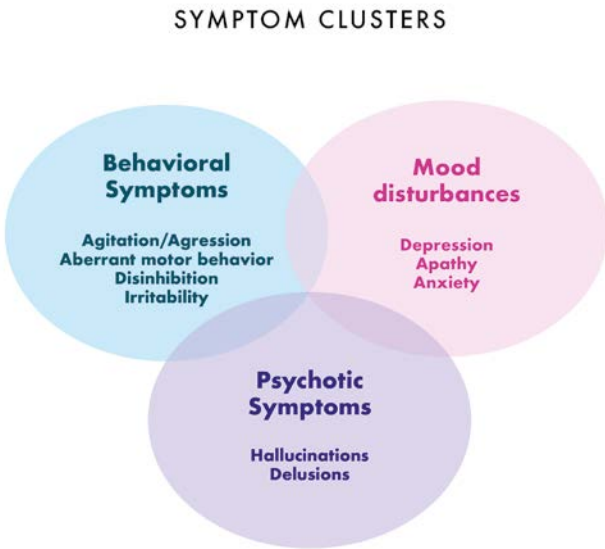

Figure 4. Clusters of NPS

NPS are a key clinical feature of dementia and constitute a major part of the disease burden. Presence of NPS has a profound effect on both patients and caregivers, diminishes the ability to perform ADL functions, while also being associate with increased hospitalization rates as well accelerated disease progression and mortality (133–140). Furthermore, NPS constitute the most important determinant of caregiver burden, contributes to an enormous need for informal caregiving and has a significant impact on health care costs, with studies indicating that up to 30% of all dementia associated costs are attributed to NPS (141–147).

1.2.1 Epidemiology of NPS

NPS in dementia are incredibly prevalent, and most patients are, to some degree, affected by non-cognitive symptoms. Data from two large American studies show that 75% of dementia patients are affected by at least one neuropsychiatric symptom, and 55 % experience two or more symptoms simultaneously, while the five-year prevalence of any NPS is 97 % (148,149). Similarly, studies conducted in Scandinavia and other parts of Europe, including dementia patients living in nursing homes, display prevalence's rates for clinically significant NPS at 72% and upwards (150–152). These studies include patient groups with different types of dementia subtypes, generating a reasonable estimate of the real-life presence of NPS. Although prevalence numbers for specific psychiatric symptoms are somewhat

fluctuating between studies, they indicate that the most common manifestations of NPS in general include depression, apathy and anxiety, with a five-year point prevalence of 77 %, 71 % and 62 % respectively (148).

In general, the majority of neuropsychiatric symptoms except for depression, seem to increase in frequency consistently over time, and their prevalence is associated with both dementia severity at baseline and disease progression (153,154). Presence of NPS has also been shown to differ depending on gender. Males show overall higher frequencies of psychiatric symptoms, especially increased levels of delusions, agitation, apathy, disinhibition, irritability and nighttime disturbances. In contrast, females tend to display higher levels of depression, whereas age is not independently associated with NPS burden (154).

1.2.2 NPS in dementia subtypes and MCI

While NPS are very frequent and affect all types of dementia, there are some differences in prevalence and trajectories of psychiatric symptoms depending on the diagnostic subgroup (154). Overall, patients with AD pathology seem to have lower levels of NPS as compared to other types of dementia, with apathy being the most common manifestation (154,155). A recent meta-analysis of NPS prevalence in patients with AD indicated that apathy, depression, aggression and anxiety are the most common behavioral disturbances, with an overall prevalence of 49%, 42%, 40% and 39% respectively (156). Previous research has also shown that disease duration, level of education and severity of cognitive symptoms are associated with increased NPS burden in patients with AD (156), and all NPS except euphoria seem to increase as cognitive function decreases (157).

Overall, AD and VaD display a relatively similar clinical profile regarding the presentation of NPS (158). Vascular type pathology is associated with more agitation and sleep disturbances as compared to AD, with depression, apathy, sleep disturbances and anxiety increasing most in severity as cognitive function declines in the setting of VaD (157,159–161). Hallucinations and delusions are more common in AD as compared to VaD (162). A diagnosis of FTD is associated with increased overall levels of NPS compared to other dementia subtypes, and symptoms such as apathy, agitation, anxiety and disinhibition seem to be especially common. Additionally, psychotic symptoms are also frequent, supporting a previously stipulated hypothesis that schizophrenia and FTD may share underlying pathological pathways (154,157,163,164). As expected, patients with DLB experience more visual hallucinations as compared to other dementia subtypes since it is a core feature of the clinical profile, but depression and anxiety are also common (154,164,165). PDD and DLB characteristically display high levels of psychotic symptoms such as delusion or hallucinations, with as much as 80% of patients showing symptoms of visual hallucination (166,167).

Studies have shown that approximately 80% of MCI patients display NPS, with depression being the most common manifestation (155). Furthermore, NPS is thought of as one of the earliest signs of preclinical AD, and presence of NPS in MCI is associated with increased risk of developing AD as well as other dementia subtypes (168,169). Additionally, the presence of any clinically significant NPS in patients, who have already developed AD, are associated with more rapid progression to severe dementia and increased mortality (136,138). Therefore it has been proposed that treatment of NPS could possibly decrease the incidence and progression of AD (136,138). Several studies have also shown that the presence of NPS, such as depression or anxiety, in cognitively healthy elderly increases the risk of developing cognitive impairment and eventually dementia (170–173). This implies that NPS are a potential clinical marker for the probability of progression from asymptomatic preclinical dementia to manifest neurodegenerative disorder.

Since the presence of NPS has been associated with increased risk of dementia development, even in the absence of cognitive impairment, researchers have proposed "mild behavioral impairment" (MBI) as a diagnostic entity (130,174). MBI is defined as mild functional impairment due to NPS, persisting for more than six months, and can be diagnosed simultaneously as MCI or as a standalone diagnosis (174). Due to the fact that neurodegenerative disorders can debut with NPS preceding symptoms of cognitive decline, the aim of the MBI diagnostic entity is to identify elderly patients with newly developed behavioral symptoms in the spectrum of neurodegenerative diseases. These patients have historically often have been misdiagnosed with psychiatric disorders, potentially providing a possibility for early detection and management of underlying dementia (174).

1.2.3 Treatment of NPS

- Non-pharmacological treatment

The first line of treatment for NPS is focused on non-pharmacological interventions such as management of physical diseases, pain, psychosocial determinants or other factors which might contribute to the presentation of symptoms in the individual patient (175–177). Specific interventions include, for example, environmental manipulation, cognitive training, acupuncture, physical exercise, aromatherapy or music therapy (133,177). For instance, environmental manipulation aims at reducing potential stressors in patient surroundings, as well as providing activities and creating set routines, hopefully resulting in less NPS burden (133).

Naturally, a key component in general treatment strategies for NPS includes management of other medical conditions such as pain, urinary tract infections, anemia or hyperglycemia, which are frequent in patients with dementia displaying NPS

and often underdiagnosed (178). Overall, the results from studies investigating the effectiveness of non-pharmacological treatment options show that these interventions are safe and show small but positive effects, although not all studies have been able to identify statistically significant results (176).

Currently, the most validated non-pharmacological treatment options include interventions provided by family members aimed at identifying modifiable risk factors for NPS, with one meta-analysis indicating effect sizes at least as good as drug treatments for behavioral symptoms in dementia (179). However, although these interventions are recommended by most experts worldwide, as the first line of treatment, they have not become routine in most health care systems which can probably be attributed to several factors, including inadequate competence among physicians as well as economic incitements (177).

- Pharmacological treatment

Several different classes of drugs have been studied and are currently used in clinical practice to reduce NPS. Still, there are to this day few medications approved by the American Food and Drug Administration (FDA) for treatment of behavioral symptoms in dementia, and most prescriptions are conducted on an off label basis (133). The most frequently used medications for pharmacological treatment of NPS include acetylcholinesterase inhibitor (AChEI), antipsychotics, mood stabilizers, NMDA-receptor modulators, benzodiazepines and antidepressants, but results regarding their efficacy have been inconsistent, and their use is often associated with significant side effects for the patients (133,180,181). Pimavanserin, an atypical antipsychotic, is approved by the FDA for treatment of psychotic symptoms in Parkinson's disease dementia (182).

Earlier reviews investigating the efficacy of pharmacological treatment for NPS have suggested the use of selective serotonin reuptake inhibitors, e.g. antidepressants, for depression specifically, but they do not seem to have any value when used for other types of NPS (183). Benzodiazepines are not recommended with the exemption of treating short term anxiety (183). Data from a meta-analysis indicates that in general, AChEIs and atypical antidepressant, are the only pharmacological interventions showing modest but statistically significant beneficial outcomes on overall NPS burden, with reduced total scores on the neuropsychiatric inventory (NPI) (184). However, this must be balanced against the increased risk of adverse events when considering the use of these medications in the dementia population (184).

Recently, more evidence is emerging regarding the possible severe side effects associated with the use of antipsychotics in patients with dementia. Several

studies have shown that the use of antipsychotics in this patient group is associated with both more rapid deterioration of cognitive function, as well as increased overall mortality (185–187). Due to these findings, the FDA has issued a "black box" warning for the use of antipsychotics in the dementia population, citing an increased risk of mortality and cerebrovascular events (188). Despite these warnings, antipsychotics are still frequently prescribed for NPS (188). Currently, AChEIs are recommended as the first line of choice for patients with mild to moderate symptoms, whereas antipsychotics should be reserved for patients with more severe NPS (184). Since current medications display modest efficacy at best and are associated with significant side effects, researchers have been searching for new potential treatment options. A few recent studies have suggested cannabinoids can be used as a potential treatment for agitation in dementia. Despite these trials showing promising effects as well as good tolerability, the data is still very limited (189–192).

1.2.4 Pathophysiology of NPS

The etiology of NPS in dementia is currently not established but is likely a consequence of complex interaction between neurobiological, genetic and environmental factors (1,131,180,193). Current combined knowledge from CSF, neuroimaging and neuropathological studies suggest that the etiology of different NPS is associated with region-specific cerebral alterations, rather than a diffuse brain pathology (193). It is crucial to have a conceptual model of the involved mediators to understand the pathological mechanism associated with NPS, and a previous review from Geda et al. (194), has proposed three theoretical frameworks for neuromodulation of behavior important to NPS.

Firstly, the frontal-subcortical circuit model suggests that at minimum three circuits connecting frontal and subcortical brain areas modulate behavior, including the dorsolateral circuit for planning or executive functions, the orbitofrontal circuit involved in inhibitory control and social functioning, as well as a circuit controlling motivated behavior. Secondly, the cortico-cortical network model hypothesizes that five different partially overlapping cortical networks govern complex behavior. Lastly, the monoaminergic model postulates that dopaminergic, serotonergic and noradrenergic neurons in the brainstem mediated human behavior through axonal projections to various areas of the brain (194). Additionally, the association between NPS and underlying dementia pathology can be conceptualized in different ways. NPS can be thought of as a direct consequence of the pathology caused by the underlying neurodegenerative disease (194). Albeit, earlier research has also proposed that NPS could precede and contribute to the development of neurodegeneration in the setting of AD, or have separate etiologies with synergistic effects, thus promoting dementia development (194).

1.2.5 Cerebrospinal fluid biomarkers

- "Core AD biomarkers"

As previously described, cerebral protein accumulation resulting in amyloid plaques and neurofibrillary tangles combined with synaptic dysfunction and neuronal death, constitute the main pathological hallmarks of AD (25). Biomarkers reflecting these AD-associated neuropathological changes can be measured in-vivo using CSF levels of total-tau (T-tau), phosphorylated-tau (P-tau) and the 42 amino acid isoform of β-amyloid protein (Aβ1-42), often referred to as "core-AD biomarkers" (195). CSF T-tau is a marker for cortical axonal degeneration and disease intensity, while P-tau reflects cerebral tangle pathology and Aβ1-42 is associated with the cerebral amyloid burden (196,197). These biomarkers can be used to assess the ongoing neurodegenerative process and typically display different profiles depending on the specific underlying neuropathological condition (198). For example, AD patients show increased levels of T-tau, P-tau and decreased levels of Aβ1-42 in CSF, as compared to healthy controls, corresponding to high overall levels of neurodegeneration and increased amounts of neurofibrillary tangles and amyloid plaques (198).

These biomarkers are used in the clinical setting facilitating correct differentiation between various dementia subtypes by increasing the diagnostic accuracy, and can also be used to identify prodromal AD in MCI patients with a specificity and sensitivity of 83 – 95 %, depending on the study cited (42,199,200). Furthermore, the ratio of Aβ42:Aβ40 is often used in the clinical setting, as it normalizes Aβ1-42 levels for total Aβ production, and thereby increases diagnostic accuracy (201). Due to the complexity and heterogeneity of dementia pathology, there is still a need for more ways to objectively quantify and asses other disease mechanisms at play. Thus, novel biomarkers are constantly being researched. Recently, markers for synaptic and axonal degeneration have become of interest, including neurogranin (Ng), growth-associated protein 43 (GAP-43) and neurofilament light protein (NFL) (195,202).

- Biomarkers for synaptic and axonal degeneration

Ng, a dendritic postsynaptic protein primarily located in cortical and hippocampal neurons involved in synaptic plasticity and long-term potentiation, has been suggested as a potential biomarker candidate reflecting synaptic dysfunction and degeneration in the setting of AD-pathology (195,203). Previous neuropathological autopsy studies have indicated that in the temporal and parietal cortex of AD patients, the full-length Ng protein is reduced, while cleavage of Ng into smaller peptides is increased (204). This results in the leakage of those Ng peptides into

CSF thought to mirror synaptic degeneration. CSF studies of Ng have demonstrated that Ng is increased in AD and MCI-AD compared with both healthy controls and other neurodegenerative disorders, thus indicating specificity for AD and a potential discriminatory role of this biomarker enabling increased diagnostic accuracy (203,205–207). A recent meta-analysis indicated that CSF Ng differs significantly between AD and healthy controls, but no difference could be observed between AD and LBD or FTD patients (208). Additionally, Ng has been shown to correlate with both amyloid and tau pathology, suggesting a link between core AD pathology and synaptic dysfunction (207,209,210).

In patients with MCI, high baseline levels of CSF Ng have also been associated with low cognitive function as well as longitudinal deterioration, and Ng seems to predict conversion from MCI to AD (205,211–213). High levels of CSF Ng in healthy patients has also been shown to predict inferior memory function and correlate to grey matter volume loss in the precuneus (214,215). Studies have shown that the ratio between neurogranin and BACE1 in CSF is correlated to the rate of cognitive deterioration in both preclinical AD, MCI and AD, while also being helpful in correctly differentiating AD from depression in patients with similar cognitive profiles (216–218). This has important clinical value since earlier research has demonstrated that amongst elderly diagnosed with a primary psychiatric disorder, 20% actually display a CSF biomarker profile compatible with AD (219). This highlights the importance of both novel biomarkers for different pathological mechanisms, and the consideration of NPS as a potential early manifestation of dementia, rather than an isolated psychiatric condition.

GAP-43 is an intracellular protein present exclusively in neurons showing high density primarily in axon terminals, thought to be involved in post-injury neuronal sprouting and regeneration, as well as axonal growth and plasticity (220). Previous neuropathological autopsy studies of AD patients have indicated that GAP-43 levels are significantly decreased, as compared to healthy controls, in the frontal cortex and some areas of the hippocampus, while other hippocampal regions display static or even increased GAP-43 activity (221–223). These findings are interpreted as a sign of synaptic dysfunction and degeneration in regions with reduced levels of GAP-43, and aberrant sprouting in brain regions with increased GAP-43 (221–223). Most CSF studies have indicated that GAP-43 levels are increased in AD as compared to both healthy controls and other dementia diseases, although one study has indicated decreased GAP-43 levels in patients with dementia as compared to healthy controls (224–227). Additionally, increased CSF GAP-43 has been correlated with both cognitive decline and increased tau and amyloid pathology in several brain regions such as amygdala, cortex and hippocampus, and low GAP-43 in the frontal cortex has been associated with increased NFT burden in patients with AD (227,228).

NFL belongs to a group of structural cytoskeletal components denoted as class IV intermediate filaments, primarily distributed in large myelinated axons, with a pivotal role in maintaining the stability of axons as well as radial growth (229). NFL increases both in CSF and blood in the presence of neuroaxonal damage independently of on the underlying pathological mechanisms, whether it be inflammation, neurodegeneration or vascular morbidity, thus making NFL a general marker for overall axonal neurodegeneration (230). Indeed, increased CSF NFL is associated with both increased overall mortality and diseases severity in dementia, and correlate with a faster rate of cognitive decline as well as brain atrophy in AD (231,232). Both AD and MCI patients show increased CSF NFL compared to healthy controls (231–237). Some interdiagnostic differences have been observed with dementia disorders affecting primarily subcortical brain areas, such as VaD, displaying increased CSF NFL levels (231–237).

In general, the knowledge regarding the association between NPS and core-AD pathological features as well as synaptic and axonal dysfunction is not clearly established. Albeit, some animal, imaging, autopsy and CSF studies have tried to examine these relationships.

1.2.6 Pathophysiology of NPS associated behavioral dysfunction

- Animal models

Several animal models using transgenic *APP/PSEN1* mice resulting in increased production of β-amyloid and rapid progression of amyloid neuropathology, including the formation of APs, have been shown to display enhanced aggression, disinhibition and altered motor activity relative to wild type controls (238–240). Thus, indicating the potential role of amyloid pathology in behavioral symptoms of NPS. Additionally, the silencing of specific serotonergic neurons in rodent brains generates increased levels of aggression (241), suggesting that the neurodegenerative process affecting these neurons could be associated with behavioral dysfunction in dementia.

- CSF studies

Few CSF studies have examined the associations between levels of core AD-pathology biomarkers and behavioral symptoms, but some evidence for their association exists, although the data is somewhat inconsistent. One CSF study found negative correlations between Aβ1-42 and aggressive behavior in AD patients, thus implying an association between amyloid pathology and behavioral symptoms (242). However, results from other studies contradict these findings (243). Agitation and irritability have also been correlated with abnormal levels of CSF Aβ1-42 in MCI patients,

and negative correlations between the total amount of NPS and Aβ1-42 have been observed, suggesting an association between amyloid pathology and NPS severity (244,245). Baseline abnormalities in CSF core AD biomarkers have also been demonstrated to predict the development of behavioral and mood type symptoms in cognitively healthy elderly, suggesting an association with AD type pathology (246). One CSF study of neurotransmitters found that in FTD patients, dopaminergic dysfunction, including increased neurotransmission and impaired modulation of dopaminergic transmission by serotonergic neurons, is associated with agitation and aggressive behavior (247). Additionally, alterations in glutamate transmission have also been associated with agitated behavior in FTD (248).

- Autopsy studies

The largest autopsy study to this date including 455 patients with pure AD pathology showed significant associations between several NPS, including behavioral dysfunctions such as agitation, and NFT burden, while no association of NPS to amyloid burden was identified (249). Given our current understanding of the cerebral regulatory mechanisms governing agitation, thought to be in part mediated by noradrenergic neurons in the LC, coupled with recent research indicating the presence of hyperphosphorylated-tau and α-synuclein inclusions in this area as one of the earliest pathological findings in AD and PDD respectively, generates a hypothesis implicating early tau-mediated pathology in subcortical regions affecting neurotransmission of monoaminergic pathways such as the noradrenergic as a potential culprit in the development of agitation (95,249–251). This hypothesis is also supported by the fact that NPS often precedes cognitive decline, which is in line with the observed early neurodegeneration in subcortical regions rather than cortical areas more responsible for cognition (95,249). Other smaller autopsy studies have indicated that agitation/aggressive behavior is correlated with increased levels of phosphorylated-tau in the frontal and parietal cortex (252) as well as increased amounts of neurofibrillary tangles in the hippocampus, orbitofrontal and anterior cingulate cortex (253,254).

Several post mortem studies have also indicated that agitation is associated with the altered cholinergic and serotonergic transmission, especially in the temporal and frontal cortex as well as hippocampus (255–258). Upregulation of serotonin re-uptake sites in the hippocampus has also been shown to correlate with aggressive behavior in AD patients (259). Of interest, presence of neurofibrillary tangles and to a lesser extent amyloid plaques, resulting in neurodegeneration and loss of serotonergic and cholinergic neurons in the nucleus raphe and nucleus basalis of Meynert, with projections to the frontal cortex are associated with the core neurodegenerative process of AD (56,260).

- Imaging studies

Neuroimaging studies of cerebral amyloid depositions, using 18F-Florbetapir-Positron emission tomography (PET), have shown that irritability is associated with increased amyloid burden in the parietal cortex amongst patients with AD (261). Studies of structural abnormalities have demonstrated associations between agitation, aggression or disinhibition and gray matter atrophy of specific brain regions including the frontal cortex, anterior cingulate cortex (ACC), posterior cingulate cortex (PCC), insula, amygdala and hippocampus, including regions of the salience network (262–265).

Hypoperfusion in regions such as left anterior temporal and right parietal cortex as well as low metabolic activity in the frontal, temporal and cingulate cortex have also been associated with agitation in AD (266–268). Agitation in EOAD has been linked to increased glucose metabolism in frontal and limbic structures, and greater resting-state functional connectivity in the anterior salience network has been associated with behavioral symptoms in AD (269,270). Furthermore, one longitudinal study of patients with preclinical AD showed that high levels of NPS, including irritability at baseline, were associated with increased glucose uptake in the PCC, ventromedial prefrontal cortex, and right anterior insula, predicting subsequent hypometabolism in the PCC after two years (271). Decreased cholinergic receptor binding in the ACC has also been associated with agitated behavior in AD (272).

Overall, current evidence suggests that behavioral symptoms in AD are associated with pathological changes in both structure and function of specific brain regions, including the frontal cortex, ACC, insula and amygdala, involved in the regulation of human behavior and salience, while also implicating that the neurodegenerative process affecting monoaminergic pathways from subcortical regions is involved in the presence of behavioral symptom in dementia (1,249,273). Furthermore, there seems to be an overlap between the core features of AD-pathology and regions associated with agitation, suggesting a possible link between the two (273).

1.2.7 Pathophysiology of NPS associated mood disorders

- Animal models

Transgenic *APP/PSEN1* mouse models have been shown to display apathy and depression-like symptoms, suggesting a potential role of amyloid pathology in the generation of mood symptoms in AD (274–276). Transgenic mice generating pronounced AD pathology displaying depression-like symptoms have also been demonstrated to have lower levels of the neurotransmitters serotonin, noradrenaline

and dopamine in the frontal cortex and ventral hippocampus (277). These areas are heavily affected by AD pathology and involved in the regulation of behavior, thus providing a link between depression and AD pathology. Additionally, animal models overexpressing β-synuclein mimicking LBD display increased levels of depression-like behavior as compared to wild type mice (278).

Transgenic mice generating AD pathology of both amyloid and tau type, display increased behaviors such as restlessness or freezing, which are interpreted as increased levels of anxiety (279). Alterations in cholinergic transmission have also been proposed as a mediator of anxiety in AD mouse models (280) and hypoactivity, which is thought to be a representation of AD induced apathy, has been reported (281). Increased levels of anxiety have also been demonstrated in animal models of vascular pathology (282) as well as in *APP* knock-in mouse models (283,284).

- CSF studies

Some studies have investigated the association between mood disorders and core AD CSF biomarkers, but generally few publications are available, and the results are inconsistent. Apathy has been shown to correlate with high levels of P-tau in patients with AD (243), whereas depression has not been found to correlate with biomarkers reflecting core AD-pathology (243,285). Anxiety in MCI patients has in one study been associated with low levels of Aβ42, whereas depression and apathy did not display any correlations with core AD biomarkers (244). A study of CSF neurotransmitters has also indicated that low levels of CSF Taurine are associated with depression as well as total levels of NPS in AD, while the ratio between dopamine and serotonin metabolites is associated with anxiety (248). Abnormal CSF levels of core AD biomarkers at baseline in cognitively healthy elderly, have also been shown to predict future development of mood disturbances, including depression and anxiety (246,286). CSF core AD biomarkers can also be used to facilitate differentiation between late-life depression, which is very common, and AD-associated depression (287). Additionally, CSF studies have indicated associations between mood disorders and neuroinflammation in AD (288).

- Autopsy studies

Autopsy studies have indicated increased amyloid and tangle burden in the hippocampus amongst patients with AD and a history of depression during lifetime (289). Increased cortical tangle burden has been observed in patients with AD and comorbid depression, as compared to AD patients without depressive symptoms, implying an interaction between AD pathology and depression (290). In the largest autopsy study to this date, mood disorders including depression and apathy showed, similarly to behavioral symptoms, clear associations with early neurofibrillary tangle pathology, whereas no associations between mood alterations

and amyloid pathology where found in patients with pure AD (249). Presence of apathy has also been associated with an increased amount of neurofibrillary tangles in the ACC in patients with AD (291).

Depression has also been linked to neurotransmitter alterations, with one study showing that selective loss of serotonergic receptors in the hippocampus is associated with increased depressive behavior (259). Loss of noradrenergic neurons in LC and serotonergic neurons in the nucleus of raphe have also been associated with depression, and the degeneration of serotonergic neurons is thought to be more severe amongst patients with AD and depression, compared to the general loss of serotonergic neurons seen in AD (1). However, some autopsy studies have failed to replicate these results, and instead imply that pathological alterations in glutamatergic neurotransmission are a potential culprit (292). These findings, combined with the evident therapeutic resistance of dementia associated depression to SSRI treatment, challenges the monoaminergic hypothesis as the cause of depression in cognitive impaired elderly (292). Instead, abnormalities in gamma-aminobutyric acid (GABA) and glutamate transmission have been proposed to be involved. Studies indicate that decreased levels of GABA, increased levels of $GABA_A$-receptors, as well as increased levels of glutamate in the frontal cortex are associated with depression in dementia (292,293).

- Imaging studies

PET studies using Pittsburgh Compound-B (PIB), a ligand for β-amyloid, have shown associations between increased amyloid burden and presence of depression in MCI patients, suggesting depression as a risk factor or early manifestation of AD (294). Another PET study on MCI patients, using a ligand for both amyloid and tangle pathology, showed that severity of depression and anxiety is associated with increased AD type pathology in the lateral temporal cortex and PCC respectively (295). Depression has also been associated with reduced grey matter volumes in the left middle frontal cortex and entorhinal cortical thickness, as well as accelerated atrophy in ACC (262,296).

AD patients with apathy have also been demonstrated to display increased amyloid burden in the frontal and right anterior cingulate cortex, as compared to AD patients without apathy (297). Similarly, apathy has been associated with increased cortical amyloid burden in MCI patients (298), and a recent review indicates that in general imaging abnormalities associated with apathy predominantly affect brain regions between the frontal cortex and basal ganglia (299). One PET study has indicated that tau-associated pathology promotes focal neurotoxicity in the orbitofrontal cortex generating apathy in AD patients (300). Atrophy of brain regions involved in arousal and reward processing, such as the prefrontal and

cingulate cortex, have been associated with apathy in AD (301,302). Interestingly, one fluorodeoxyglucose (FDG)-PET study has indicated that apathy is associated with different neuroanatomical sites in AD as compared to behavioral FTD (303). Additionally, one imaging study has suggested that reduced dopamine transporter uptake in putamen is associated with apathy in dementia (304).

1.2.8 Pathophysiology of NPS associated psychotic symptoms

- Animal models

There is currently limited data on animal models for psychotic symptoms in dementia. To this date, only one study using animal models of dementia pathology has investigated the association between psychotic symptoms and the neurodegenerative process associated with dementia (305). Transgenic mice generating tau-type pathology in frontal cortex and hippocampus displayed correlations between psychotic phenotype and insoluble P-tau, suggesting a link between tau mediated neurodegeneration and psychosis in AD (305).

- CSF studies

CSF studies have also indicated the contribution of tau-associated neurodegeneration in psychotic symptoms of AD. One longitudinal CSF study on AD patients has shown that high levels of T-tau at baseline, but not P-tau and Aβ1-42, were associated with an increased probability of developing psychotic symptoms (306). Levels of CSF dopamine metabolites have also been shown to exhibit a negative association with hallucinations in DLB patients (248).

- Autopsy studies

In line with animal and CSF studies, psychotic behaviors have been associated with a higher burden of tau pathology. In one study, patients with AD and psychotic symptoms had a more than a twofold increase of neocortical NFTs, as compared to AD patients without psychotic behavior (307). Similarly, one study has indicated that psychotic AD patients have increased concentrations of intraneuronal P-tau in the prefrontal cortex, as compared to non-psychotic AD patients (308). Of interest, in one autopsy study, the associations between high levels of P-tau in the frontal cortex and psychotic symptoms was only observed in female AD patients, whereas in males psychotic behavior was associated with α-synuclein pathology (309). Cholinergic alterations have also been proposed to be involved, with increased density of muscarinic receptors in the frontal and temporal cortex displaying an association with psychotic symptoms in AD (310). Increased D3 receptor density in nucleus accumbens has also been associated with psychosis in

AD (311). Reduced levels of serotonin, as well as the ratio between serotonin to acetylcholinesterase, have also been associated with psychosis in AD (256,312). Additionally, increased cortical β-amyloid (1-42)/β-amyloid (1-40) ratio has been correlated with psychosis in AD, suggesting a role of soluble forms of Aβ in the pathogenesis of psychosis in AD (313).

- Imaging studies

Imaging studies using PET have shown that alterations in dopamine transmission, including increased D2/D3 receptor availability in the striatum, are associated with delusions in AD (314). Neuroimaging studies have demonstrated that psychosis in AD is associated with decreased perfusion, hypometabolism and reduced grey matter volume in areas such as the frontal cortex and ACC. However, these results are somewhat inconsistent (273,315). Additionally, the atrophy rate of the frontal cortex, parietal cortex and ACC has been associated with manifest psychotic symptoms during longitudinal follow-up (316).

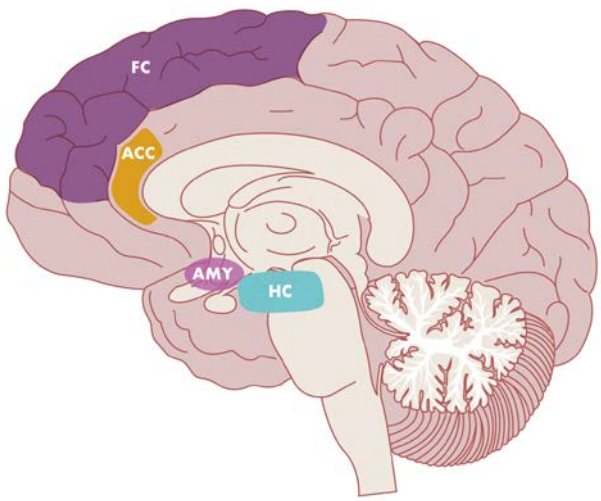

Figure 5. Brain areas associated with NPS. FC = frontal cortex, ACC = anterior cingulate cortex, AMY = amygdala, HC = hippocampus

1.3 Clinical measurements of NPS and cognition

Assessment of NPS is usually conducted through one on one interviews between health care providers and patients, or the patient's relatives and caregivers, using different clinical rating scales. Correct measurement and description of NPS constitutes a foundation for both research and clinical practice in this area. Several different measurement scales have been developed for this purpose. The Neuropsychiatric Inventory (NPI) is currently considered the gold standard for measurement of NPS and is one of the most validated rating scale used in modern medical practice (317). In the studies included in this thesis, the NPI was used to assess both overall levels and subtypes of NPS. Additionally, the Cohen-Mansfield agitation inventory (CMAI) was used to specifically asses levels of agitation and aggressive behaviors (318).

1.3.1 Neuropsychiatric Inventory

The NPI is globally the most used tool to assess NPS in dementia, and several versions have been developed and translated into multiple languages (319). The most prevalent version of NPI consists of 12 different domains assessing various NPS including; hallucinations, delusions, agitation/aggression, dysphoria/depression, anxiety, irritability disinhibition, euphoria, apathy, motor disturbance as well as changes in night-time behavior or appetite and eating patterns (320). The NPI is a structured interview which is completed by a trained clinician interviewing an informant, in most cases, the patient's caregiver or other relatives familiar with the patient. The NPI includes 12 items and assesses both frequency and severity of symptoms as well as caregiver distress. Every domain is scored based on frequency (1-4 points) and severity (1-3 points) of NPS during the last month, and the scores are then multiplied do give a total domain score of maximum 12. The total score is then obtained by adding the individual domain scores, allowing a minimum of 0 and a maximum of 144 points on the NPI scale. In both research and clinical practice, the total NPI score (0-144) and domain-specific scores (0-12) are used.

1.3.2 Cohen-Mansfield Agitation Inventory

The CMAI is a questionnaire for the assessment of agitation in dementia and is administered by health care professionals with the patient's caregivers. CMAI consists of 29 items describing different emotional and behavioral disturbances, specifically related to agitated behavior (318). Every item is rated based on frequency 1-7, with 1 being never and 7 corresponding to the presence of agitated behavior on an hourly basis, with higher scores thus reflecting increased agitation. The total CMAI score is then calculated as the sum of the 29 different frequency scores, with a maximum score of 203 points.

The results from the CMAI questionnaire can be assessed as the total sum (CMAI-total) or divided into four different cluster-scores relating to different subtypes of agitation. Sub-item 1 measures aggressive physical behavior such as kicking or hitting. Sub-item 2 measures non-aggressive physical behavior including, for example, pacing, hoarding or general restlessness. Sub-item three measures aggressive verbal behavior such as screaming or cursing, while sub-item 4 measures non-aggressive verbal behavior, including symptoms such as complaining or negativism. The cluster-scores are not considered as distinct entities but rather as different manifestations of agitation. Both the CMAI-total score and the four cluster scores were used in the statistical analysis in this thesis.

1.3.3 Mini Mental State Examination

Several different clinical tests intended to measure cognitive function and decline in the context of dementia have been developed. These tests assess different cognitive domains such as executive functioning, memory or visuospatial abilities. They are often used as screening tools for dementia amongst patients presenting with memory complaints or other symptoms, indicating the possibility of dementia. In Swedish healthcare, the most commonly used screening tool for cognitive impairment is the Mini Mental State Examination (34), although other tests such as the MoCA are also often used (33). A recent Cochrane review has shown that the sensitivity and specificity of MMSE for detecting dementia is 0.85 and 0.90, respectively (321). In this thesis, MMSE was the primary tool for quantification of cognitive status.

MMSE is a clinician-administered test that can be used for the assessment of cognitive function in dementia, or when screening for cognitive impairment in patients. It is also suitable for the assessment of dementia stages and disease progress. The test consists of 20 different tasks or questions, designed to identify impairment in 11 specific cognitive domains such as memory, executive functions or orientation. The maximum score is 30 points, and a result of 24 or less is considered pathological and potentially indicative of dementia. Although, it is important to consider that patients with high cognitive capabilities at baseline may experience significant cognitive impairment while still score within the normal range on MMSE, suggesting the need for higher cut off scores in patients with high education (322). Other relevant rating scales in the context of dementia include the Clinical Dementia Rating scale, which assesses cognitive functioning but also aspects of ADL, or the Cornell scale for depression in dementia for quantification of depressive symptoms (323,324)

2 AIMS

The overall aim of this thesis was to study the relationship between neuropsychiatric symptoms in dementia and core CSF AD biomarkers (Aβ1-42, T-tau, P-tau), as well as biomarkers for synaptic and axonal injury (Ng, GAP-43 and NFL). Secondary aims included investigation of the effect of current treatment options on NPS and CSF biomarker profile.

The primary aims, according to the study, were:

- **Study I:** To examine the association between core AD biomarkers and agitation in dementia.
- **Study II:** To compare treatment effects between Galantamine and Risperidone on agitation in people with dementia.
- **Study III:** To investigate the effect of Galantamine and Risperidone on the core AD CSF biomarker profile.
- **Study IV:** To examine the association between Ng, GAP-43 and NFL in CSF and neuropsychiatric symptoms in dementia.

3 MATERIALS AND METHODS

3.1 Ethical approval

Informed consent was obtained from all patients or if necessary, the patients' legal representative. The regional Ethics Committee of Karolinska Institutet, Stockholm Sweden, approved the study. Registration number: 441/01 at Karolinska Institutet.

3.2 Study population

Data from two different study populations have been included and used in the papers constituting this thesis. The predominantly used dataset (*study I to IV*) comes from patients originally included in a randomized controlled trial to compare the effect of Galantamine and Risperidone on NPS in dementia (325). This patient cohort is included in all four papers and will be referred to as the NPS-cohort. In the fourth and last paper, an additional patient group was sampled from the GEDOC database at Karolinska University Hospital to obtain healthy controls as well as AD patients with low levels of NPS. This study population will be referred to as the GEDOC-cohort.

3.2.1 Inclusion and exclusion criteria

- NPS-cohort

One hundred and forty-five community-dwelling patients, referred from general practitioners to the memory clinic at the Department of Geriatric Medicine at Karolinska University, due to suspected dementia and presence of NPS between January 2003 and September 2005 were available for inclusion. Out of the referred patients 100 of age 45 or older, who fulfilled the criteria according to the Diagnostic and statistical manual of mental disorder, Fourth Edition (DSM-IV) (326) for diagnosis of AD with behavioral disturbance, VaD with behavioral disturbance, MIX with behavioral disturbance, PDD with behavioral disturbance, FTD with behavioral disturbance or presence of MCI were included in the study. For inclusion, patients also had to have a total score of at least 10 on the NPI with symptoms present during the last two weeks. Patients were excluded if they had a diagnosis of schizophrenia or other psychiatric disorders, a history of seizures, alcohol abuse and clinically significant hepatic, renal, pulmonary or metabolic disturbances.

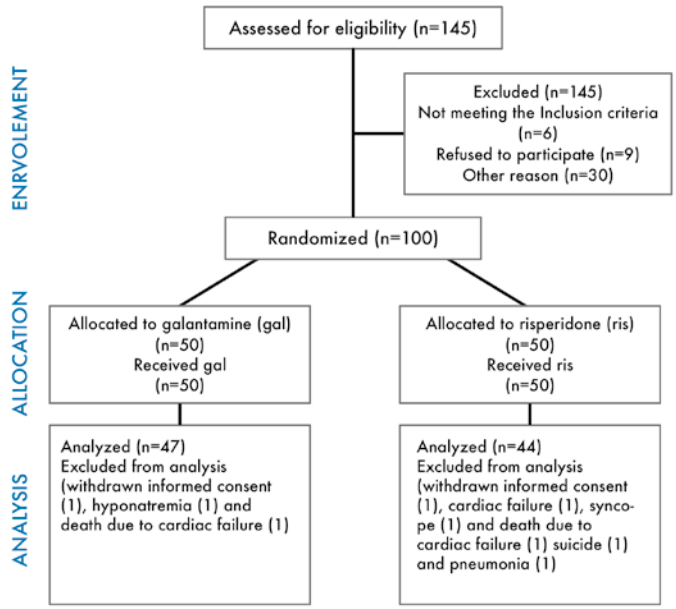

Figure 6. Flowchart for NPS-cohort

- GEDOC-cohort

GEDOC is a research database and biobank at the memory clinic, Karolinska University Hospital, including clinically well-characterized patients assessed for dementia due to memory complaints at the clinic. The database contains information regarding different variables such as diagnosis, CSF biomarkers, MMSE scores as well as CSF samples, created to facilitate research in the field of dementia. A total of 60 patients, assessed between 2003-2015, were recruited from the GEDOC database out of a total of 13300 existing subjects in the system. Thirty of these patients were diagnosed as subjective cognitive impairment (SCI), with normal MMSE scores and normal CSF AD-biomarker profile, defined as Aβ1-42 > 500, T-tau <400, P-tau <80 ng/ml. These patients were referred due to subjective memory complaints but assessed as cognitively intact with no evidence of neurodegenerative disorder, and thus included and treated as healthy controls. Additionally, thirty patients diagnosed with AD displaying an AD positive biomarker profile, i.e. Aβ1-42 < 500, Tau >400 and P-Tau >80 ng/ml, but without neuropsychiatric symptoms and an MMSE score equal or more than 16 but less than 24 were included. Patient's medical records were reviewed, and subjects were excluded from the study if any significant NPS were mentioned. This patient subgroup is referred to as the "AD low NPS" group (Figure 7).

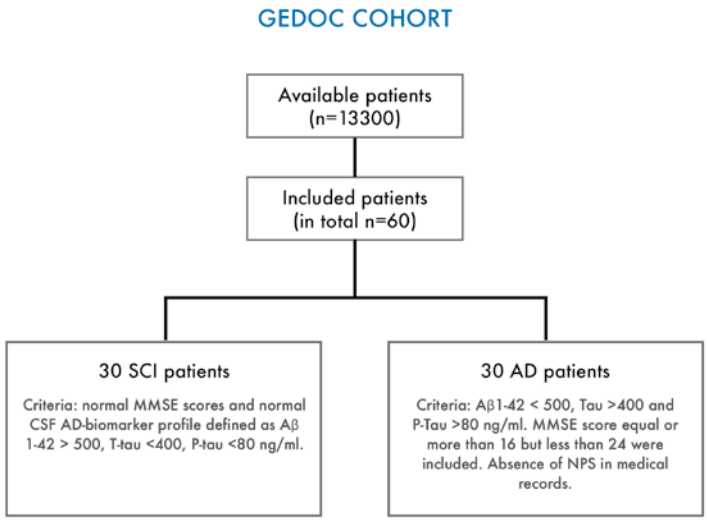

Figure 7. Flowchart for GEDOC-cohort

3.2.2 Clinical assessment

- NPS-Cohort

After inclusion, all patients underwent baseline evaluation of neurological, physical, behavioral and neurocognitive status, which was repeated during follow-up after 3 and 12 weeks. Initial diagnostic procedures included somatic, psychiatric, neurological and neuroimaging (computed tomography scans) examination performed by a licensed specialist in geriatric medicine with experience in dementia. Lumbar puncture for collection on CSF was conducted at baseline and after 12 weeks. During each visit, a medical examination including psychiatric and neurological status was conducted, and standardized scales of cognition (MMSE) and neuropsychiatric symptoms (NPI, CMAI) were administered, in each instance by the same specialist in geriatric medicine (YFL). One hundred patients were included with the following distribution of dementia diagnoses; 34% AD, 27 % MIX, 18 % VaD, 3 % FTD, 2 % PDD, 4 % unspecified dementia and 12 % MCI.

- GEDOC-Cohort

Patients in the GEDOC-cohort were assessed by staff at the memory clinic, Karolinska University Hospital, according to standard operating procedures within Swedish health care. Data was collected from the electronic database, including variables such as diagnosis, CSF AD biomarkers, MMSE score, and NPI scores.

Frozen CSF samples from all patients were obtained. Due to insufficient data regarding rating scales for NPS (NPI) on the thirty included AD patients, their medical records were revived, and patients were excluded if significant mentions of NPS were observed.

3.2.3 Randomization and intervention (NPS-cohort)

Included patients were consequently randomly allocated to one of the two treatment groups according to a pre-defined randomization code. The initial dosage of Galantamine was 4 mg twice daily, increased to 8 mg twice daily after one week and to 12 mg twice daily at the start of week three. Subjects randomized to Risperidone treatment received 0.25 mg twice daily at the start. After one week, the dose was increased to 0.5 mg twice daily, and at the start of the week, three patients received 1.5 mg daily. Compliance was monitored by quantifying unused medication and via self-reports of patients and caregivers. To decrease bias, the study clinician performing the rating scales of NPS was unaware of the treatment arm at the time of clinical assessment.

3.2.4 Follow-up (NPS-cohort)

After initiation of the clinical trial, a total of nine patients dropped out during follow-up between baseline and week 12 (six patients in the Risperidone group and three patients in the Galantamine group). Reasons for withdrawal from the study as well as study design can be seen in Figure 6.

3.2.5 CSF analysis

- NPS-cohort

CSF samples were collected at baseline and after 12 weeks using standard operating procedures according to Swedish health care standards at the memory clinic, Karolinska University Hospital. Lumbar punctures were performed and the collected CSF (6 ml) stored in polypropylene tubes. The first 2 ml of every sampling was discarded, and the rest was centrifuged at 3000 rpm for 10 min at 4C+ and frozen in aliquots of 2 ml at -70C. From the 100 included patients in the NPS-cohort, 95 successful lumbar punctures were performed at baseline. This was because three patients refused the procedure, one had an arachnoid-cyst, and one sampling was unsuccessful due to muscular rigidity. The collected CSF was analyzed at the Department of Neurochemistry, Mölndal Hospital, by Kaj Blennow and collaborators.

CSF T-tau concentration was determined using a sandwich ELISA (Innotest hTAU-Ag, Innogenetics, Gent, Belgium) constructed to measure all tau isoforms regardless of phosphorylation status. Tau phosphorylated at threonine 181 (P-tau181) was measured using a sandwich ELISA method (INNOTEST® PHOSPHO-TAU, Innogenetics, Ghent, Belgium). Aβ1-42 levels were determined using a sandwich ELISA (INNOTEST® ß- AMYLOID (1-42), Innogenetics, Gent, Belgium) constructed to measure Aβ containing both the first and 42nd amino acid. These are commercially available ELISA kits frequently used in research for measurement of dementia biomarkers and validated through several studies (327–329), all tests were executed according to the manufacturer's instructions.

CSF levels of Aβ42 and Aβ40 to calculate the Aβ42/40 ratio were measured using the MSD Abeta Triplex assay (MSD, Rockville, MD), using a multiplexed method. CSF Ng was measured using an in-house ELISA method, as described previously in detail (207) using the monoclonal antibody NG2 (epitope 52–63) but with the monoclonal antibody NG22 exchanged for NG36 (both having the epitope Ng 63–75). CSF GAP-43 and NFL were analyzed by in-house ELISA methods as previously described in detail (227,330). All samples were analyzed by board-certified technicians, using one batch of reagents, following strict rules for quality control (331).

- GEDOC-cohort

CSF levels of Aβ1-42, T-Tau, P-Tau were obtained from the GEDOC database (n=60). These CSF samples were collected and analyzed using the same clinical producers and technical methods as for the NPS-cohort, and the same staff performed lumbar punctures as in the NPS-cohort. Additionally, stored and frozen CSF samples from these patients were obtained and analyzed for levels of Ng, GAP-43 and NFL by the Department of Neurochemistry, Mölndal Hospital, using the same staff and methods as for the NPS-cohort.

3.2.6 Statistical methods

The majority of the investigated variables (CSF biomarkers) included in the four studies did not display normal distribution or equal variance. Therefore, in general, non-parametric statistics were used as the primary analytic method, but parametric methods were used when appropriate and considered acceptable due to sufficient sample size. Descriptive data are presented as medians and interquartile range (IQ) if not stated otherwise, and a p-value <0.05 was regarded as statistically significant. The Statistica ® 10.0 (study I-III) and ® 13.0 (study IV) software package (StatSoft, Tulsa, Oklahoma, USA) was used for all statistical analysis.

Study I

In this study, we used Spearman rank correlations to investigate associations between baseline values of CSF AD-biomarkers (Aβ1-42, T-tau and P-Ttu) and CMAI, within the whole cohort and also within different diagnostic groups. Positive findings were then validated using a linear regression model adjusting for confounder's age, gender and cognition (MMSE).

Study II

In this clinical trial, we primarily used repeated measures ANCOVA to compare the efficacy of Risperidone vs Galantamine on the main outcome variable total CMAI. Furthermore, we conducted dependent and independent T-tests to compare the within and between-group differences to strengthen the robustness of the results.

Study III

In this study, we investigated the effect of treatment with Risperidone and Galantamine on the CSF profile of core AD-biomarkers. Dependent and independent T-tests were used to compare between and within-group differences in biomarker levels post-treatment. We also created a general linear model including biomarkers, age, gender, dementia diagnosis and treatment type to see if any of these variables could predict a change in NPI or CMAI between the start and follow-up.

Study IV

In this study, we investigated the relationship between biomarkers Ng, GAP-43, NFL and NPS in dementia. Mann-Whitney U test was used to compare CSF biomarker levels between AD patients with high vs low NPS burden. Spearman rank correlation test was used to assess the associations between biomarker levels and NPS. Factorial ANOVA was used to analyse differences in biomarker levels depending on diagnosis and *APOE*-status, as well as potential interaction effects. ANCOVA analysis was then performed to adjust for confounders, including age and gender.

4 SUMMARY OF RESULTS

4.1 Demographics

The baseline clinical and demographical characteristic of the study population from the NPS-cohort and GEDOC-cohort (SCI and AD low NPS groups) are presented in Table 1. The included patients were relatively equally distributed between the different diagnostic subtypes with regards to clinical characteristics, except for the expected higher MMSE score in MCI and SCI groups, as well as age which was substantially lower in the SCI group. In table 1, the nine patients diagnosed with FTD (n=3), PDD (n=2) and unspecified dementia (n=4) are compounded into one group denoted "Other" (n=9).

Table 1. Demographic, clinical and CSF characteristics of the groups

	All n=160	AD total n=64	ADHNPS n=34	ADLNPS n=30	SCI n=30	MCI n=12	MIX n=27	VaD n=18	Other n=9
Age, years	76(19)	78 (16)	80 (8)	70 (19)	60(7)	82 (7)	83 (6)	76 (9)	68 (21)
Females (n)	99	39	20	19	13	10	19	11	7
***APOE*-status ε4 pos / total n**	78/149	37/54	24/34	13/20	7/29	4/12	14/27	10/18	6/9
MMSE 0-30 points	22 (7)	20 (5)	20 (6)	21 (2)	30 (1)	26 (3)	20 (5)	22 (6)	16 (6)
NPI-total n=100	51 (39)	42 (29)	42 (29)	m.d	m.d	56 (48)	47 (52)	46 (26)	50 (33)
CMAI-total n=100	47 (17)	44 (15)	44 (15)	m.d	m.d	43 (20)	51 (21)	45 (15)	48 (11)
Cornell n=144	4 (5)	4 (5)	5(5)	2 (5)	4 (4)	6 (5)	5 (4)	6 (4)	4 (1)
T-tau pg/ml n=155	681 (420)	698 (391)	680 (400)	719 (470)	265 (92)	730 (430)	695 (220)	550 (330)	505 (360)
P-tau pg/ml n=155	90 (55)	98 (37)	87 (52)	104 (31)	45 (18)	99 (48)	97 (39)	74 (33)	66 (41)
Aβ1-42 pg/ml n=155	528 (250)	410 (133)	440 (170)	396 (84)	805 (200)	490 (250)	435 (160)	460 (220)	535 (170)
Aβ 42/40 pg/ml n=96	0.5 (0.2)	0.4 (0.2)	0.4 (0.2)	m.d	m.d	0.4 (0.2)	0.4 (0.2)	0.5 (0.2)	0.6 (0.4)
Ng pg/ml n=155	249 (151)	279 (142)	249 (148)	295 (86)	175 (85)	314 (223)	244 (177)	218 (119)	193 (148)
GAP-43 pg/ml n=155	3633 (2211)	4065 (2077)	3901 (2190)	4229 (1818)	2357 (964)	3955 (2586)	3639 (2750)	3698 (741)	3582 (853)
NFL ng/ml n=153	1580 (1480)	1670 (1360)	1970 (1540)	1455 (710)	620 (420)	1770 (1500)	2150 (1620)	1780 (1800)	2510 (2800)

Data is presented as medians and IQR. Abbreviations; m.d = missing data, ADHNPS = AD high NPS, ADLNPS = AD low NPS. GEDOC-cohort includes the "AD low NPS" and SCI group. NPS-cohort incudes the "AD high NPS", MCI, MIX, VaD and "other" group. AD total includes both the AD high and AD low NPS group.

4.1.1 Associations between CSF biomarkers and NPS

In *study I,* we found associations between agitation and high levels of P-Tau (r= 0.35, p=0.05) and T-tau (r=0.36, p = 0.04) in patients with AD. No significant correlations were established when analyzing the whole cohort, nor in any of the other dementia subgroups, and no significant correlation was found between Aβ1-42 and agitation. When adjusted for age, gender and MMSE-score, both P-tau and T-tau still displayed significant associations with CMAI-total in AD (p=0.04 and p=0.01 respectively). The analysis also showed that a one unit increase of T-tau results in a 0.008 increase in CMAI-total, while a one unit increase of P-tau was associated with a 0.11 unit increase on the total CMAI score.

In *study III,* when analyzing all patients, we found that low levels of CSF Aβ1-42 at baseline was a significant predictor of change in irritability (Beta = -0.43, $p < .05$) during follow-up. Additionally, baseline levels of CSF Aβ1-42, Aβ42/40 and P-tau were shown to be significant predictors of change in the NPI subitem assessing appetite and eating disturbances (Beta = 0.52, $p < .05$, Beta = -0.46, $p < .05$ and Beta = 0.32, $p < .05$ respectively).

In *study IV*, we did not observe any significant differences in CSF levels of biomarkers for synaptic (Ng, GAP-43) and axonal (NFL) injury between AD patients with high vs low levels of NPS when adjusted for age. Although, in patients younger than 70 years of age, a trend towards a statistically significant decrease of Ng in AD patients with high levels of NPS was observed as compared to AD patients with low levels of NPS (p=0.06, Mdn 309 vs 179). Furthermore, no significant associations were observed between NG, GAP-43, NFL and NPS amongst AD patients. In contrast, amongst VaD patients, hallucinations showed associations with GAP-43 (r=-0.54, p=0.02) and NFL (r=-0.53, p=0.03) while disinhibition was associated with GAP-43 (r=-0.77, p=0.01) and Ng (r=-0.58, p=0.02). Additionally, significant correlations were observed between NFL and delusions in MIX patients (r=0.43, p=0.04) and between Ng and anxiety in MCI patients (r=0.64, p=0.04).

4.1.2 Clinical effects of Risperidone and Galantamine on NPS

Study II demonstrated that both Risperidone and Galantamine were associated with reduced levels of agitation in patients with dementia. When compared head to head, Risperidone showed a significant treatment advantage over Galantamine, both at week 3 (mean (CMAI) difference 3.7 points, p=0.03) and at week 12 (4.3 points, p=0.01). Although, treatment with Risperidone was also associated with more adverse events and hospitalizations, as well as a higher dropout rate in comparison with Galantamine.

4.1.3 Effects of drug treatment on CSF biomarkers

In *study III*, we showed that treatment with Risperidone was associated with a significant decrease in Aβ1-42 between baseline and follow-up. There were no significant differences in biomarkers P-tau, T-tau, Aβ42/40 and Aβ1-42 between the two treatment groups at baseline nor at follow-up. Within the Risperidone group, CSF Aβ1-42 levels in patients were significantly decreased at follow-up, showing an 8% (40 pg/mL) reduction as compared with baseline (p=0.03).

4.1.4 Relationship between biomarkers for synaptic and axonal injury and diagnosis, *APOE*-status and gender

In *study IV*, results from ANCOVA analysis indicated that CSF Ng level was not significantly associated with diagnostic subgroup (p=0.10). In contrast, female sex (p=0.02) and the presence of *APOE* ε4 (p=0.01) was associated with increased levels of Ng. In contrast, GAP-43 was not associated with either diagnosis, *APOE*-status, or gender. Analysis of NFL showed that CSF levels differed depending on diagnosis, with lower levels in the SCI group as compared to AD, MIX and VaD ($p<0.05$). Gender and *APOE*-status did not affect CSF levels of NFL.

4.1.5 Association between core AD biomarkers and synaptic and axonal dysfunction

In *study IV,* we have shown that biomarkers for synaptic dysfunction (Ng, GAP-43) are strongly correlated with biomarkers for tau-associated pathology, i.e. T-tau (r=0.73 p=.01 and r=0.84, p=.01 respectively) and P-tau (r=0.75, p=.01 and r=0.82, p=.01 respectively) when analyzing the whole cohort (study IV). These correlations remained significant in every diagnostic subgroup except GAP-43 and P-tau (p=0.06) in the VaD group. NFL was associated with T-tau (r=0.54, p=0.01) and P-tau (r=0.48, p=0.01) in the whole cohort, but during subgroup analysis the association only remained significant in the "AD high NPS" group (r=0.44. p=0.01 and r=0.52, p=0.01 respectively). Aβ1-42 was significantly associated with Ng (r=-0.34, p=0.01), GAP-43 (r=-0.44, p=0.01 and NFL (r=-0.39, p=0.01) in the whole cohort, but these correlations did not retain their significance in any of the diagnostic subgroups.

5 DISCUSSION

5.1 Is core AD pathology associated to NPS?

One of the aims of this thesis included investigation of the relationship between core AD pathology, as measured by CSF biomarkers P-tau, T-tau, Aβ42/40 and Aβ1-42 reflecting key pathological mechanisms associated with AD, and presence of NPS. Our findings suggest that tau associated pathology, disease intensity and cortical axonal degeneration, as reflected by increased levels of CSF P-tau and T-tau, may be of importance for the development of agitation in AD patients. These associations were not found in patients with other types of dementia pathology, suggesting specificity for AD, and other pathological mechanisms should be explored in the setting of other dementia diseases. This is congruent with several earlier studies showing that agitation is associated with increased levels of phosphorylated tau and NFT burden in frontal, temporal orbitofrontal and anterior cingulate cortex as well as the hippocampus (252–254).

These brain regions, known to be affected in AD pathology, overlap with brain regions involved in cortico-subcortical networks mediating salience and behavior, thus generating a link between tau-associated pathology and NPS. Additionally, early NFT pathology in subcortical regions, including brainstem and hypothalamic nuclei in Braak stages I-II, has been associated with the presence of multiple NPS including agitation, thus implying tau-associated pathology as a key promoter of NPS in AD (249). These results also provide a mechanistic link between the proposed monoaminergic model of NPS and AD pathology. For example, loss of noradrenergic neurons in the LC, known to generate agitated behavior, due to tau-driven neurodegeneration is an established phenomenon in AD (249,250). Additionally, the loss of cholinergic neurons in the nucleus basalis of Meynert with projections to the cingulate cortex or amygdala, due to predominately tau-associated pathology, is also a finding in early AD pathology. Thus, providing further evidence linking the core neurodegenerative process of AD with alterations in monoaminergic pathways to regions known to be involved modulation of behavior (260,273).

In contrast with our findings, one previous CSF study failed to show any association between agitation and T-tau or P-tau in AD patients (243). Speculatively, this can be attributed to the fact that the included study population was not specifically selected based on the presence of NPS, and thus overall displayed low levels of psychiatric symptoms. Additionally, the NPI subitem was used to assess agitation as compared to CMAI in our study. In general, there is increasing evidence suggesting that tau-driven neurodegeneration is involved in the pathogenesis of NPS in AD.

The role of amyloid pathology in NPS is currently more ambiguous, and we did not observe any associations between Aβ1-42 and agitation (*study I*). Although baseline levels of Aβ1-42 and Aβ42/40 correlated with longitudinal change in NPI sub items assessing irritably and eating disorders (*study III*). Earlier animal models of AD with pronounced amyloid pathology have indicated increased behavioral disturbances, although translation and inference of such findings to humans is notoriously difficult (238–240).

Previous CSF studies have also been inconsistent, with one study finding significant but weak negative associations between Aβ1-42 and agitation as measured with the Behave-AD scale (242). A possible explanation for this discrepancy could be that, in contrast with our study, no adjustment for cognition was included which may have confounded the results. A more recent CSF study using NPI to assess agitated behavior could, in line with our results, not replicate this finding (243). Imaging studies of cerebral AP burden using PIB have found associations between apathy and increased amyloid retention, but not with any other NPS further supporting the limited role of amyloid pathology in NPS (297). Although, one CSF and one imaging study, found that low levels of Aβ1-42 or high amyloid burden at baseline in cognitively intact elderly were associated with increased development of NPS during longitudinal follow-up (246,332). These findings would imply that amyloid associated pathology, at least to some degree, is associated with development of NPS. Given the evident role of amyloid pathology in AD, it is plausible to consider that Aβ is somehow involved the genesis of NPS, possibly as an upstream stimulator of neurodegeneration. However, considering recent evidence, NPS could likely be explained by simultaneous tau-driven neurodegeneration of subcortical structures (249).

5.1.1 Is synaptic and axonal dysfunction associated to NPS?

Since synaptic and axonal injury are evident contributors to AD neuropathology (333), we wanted to investigate whether CSF biomarkers reflecting such alterations are related to the clinical phenotype of NPS. When comparing CSF levels of Ng, GAP-43 and NFL between AD patients with high vs low NPS burden, we initially saw that patients with high levels of NPS had increased NFL and decreased Ng in CSF, although when adjusting for age no significant difference could be observed. However, in AD patients younger than 70 year of age with high levels of NPS we observed a trend towards significantly decreased levels of CSF Ng as compared to the AD low NPS group. We also performed a correlation analysis between NPS, as measured by NPI score, and markers for synaptic and axonal injury (Ng, GAP-43, NFL). In general, few statistically significant associations were observed, and in the AD subgroup, no significant correlations could be seen with any of the NPI sub items. In contrast,

we observed multiple significant negative associations between these biomarkers and NPI subitems assessing hallucinations and disinhibition in patients with VaD.

To this date, few CSF studies have investigated the relationship between synaptic dysfunction and NPS. Some animal, as well as imaging studies, have implicated associations between synaptic dysfunction and NPS (270,334,335). Historically, imaging studies using FDG-PET measuring glucose metabolism have been used as a surrogate to measure synaptic dysfunction in-vivo (336). Several studies have found associations between NPS and decreased glucose metabolism in brain regions such as the frontal and cingulate cortex (267,337–340). Although it is important to consider that the use of glucose metabolism as a marker for synaptic dysfunction has some limitations (336). For example, glucose uptake occurs in astrocytes surrounding synapses. Thus, hypometabolism may reflect changes in these structures (336). Recently, a novel imaging ligand (11C-UCB-J) has been developed with binding affinity for synaptic vesicle glycoprotein 2A, a presynaptic protein (341). This enables the direct measurement of synaptic density, generating interesting future research possibilities. Of importance, improved synaptic imaging modalities may facilitate research on the temporal and spatial relationship between synaptic dysfunction, tau-, and amyloid-associated pathology, possibly the largest knowledge gap in our current comprehension of AD.

As reported and discussed in *study IV*, we report some evidence implicating synaptic dysfunction, as measured with CSF biomarkers (Ng, GAP-43, NFL), in the role of NPS. Especially implicating an association between NPS of the psychotic spectrum and synaptic dysfunction in the setting of vascular pathology. Furthermore, we found an indication that high levels of CSF Ng may be associated with decreased NPS in early AD. One other study has also indicated that high CSF levels of Ng in MCI patients may be associated with a decreased rate of cognitive decline, while the opposite relation was seen in AD patients (342). Speculatively, fluctuations of CSF Ng could have different biological mechanisms in different stages of the neurodegenerative process in AD. Future research should focus on incorporating both imaging and CSF measures of synaptic dysfunction in order to establish a deeper understating of both anatomical and structural deficits in synaptic functioning during dementia.

5.1.2 Can AChEIs or atypical antipsychotics be used for treatment of NPS?

Treatment of NPS is a major challenge from a clinical standpoint with current medications showing modest value at best, while NPS cause severe distress for both patients and caretakers (141,144,184). We have demonstrated that both Galantamine, an AChEI, and Risperidone, an atypical antipsychotic, were associated with reduced levels of agitation in dementia. Risperidone treated patients showed

a significantly larger improvement during follow-up as compared to Galantamine treated patients. However, the increased treatment effect of Risperidone has to be counterbalanced by the decreased tolerability. Patients receiving the antipsychotic manifested higher numerical, albeit not statistically significant, dropout rate, hospitalizations and adverse compared to Galantamine treated patients. This is in line with recent systematic reviews and guidelines suggesting that atypical antipsychotics show modest efficacy in general. Therefore, they should only be used when patients display agitated behavior of such magnitude, that poses a risk for physical harm for them or others and the first line of therapy is insufficient (2,343,344).

Use of atypical antipsychotics in the dementia population is, based on several earlier studies, known to cause an increased risk of cerebrovascular events and increased total mortality leading to a "black box" warning issued by the FDA in 2005 (345–347). A recent large American case control study, including more than 90 000 patients with dementia, showed that treatment with Risperidone was associated with a 3.7 % increased risk of death compared to matched controls with dementia not receiving antipsychotics. This is a fourfold increase in risk compared to estimations from earlier studies (348). High doses of antipsychotics were associated with 3.5% increased risk of mortality as compared to low doses, suggesting a dose-dependent relationship with regards to mortality (348). Additionally, an extensive 2018 meta-analysis including both patients with (n = 380 000) and without (n = 359 235) dementia, found that the use of antipsychotics was associated with a twofold increased risk of mortality (RR=2) in all patients (349). This study also confirmed the dose-dependent relationship, while indicating that the risk of death is mostly elevated during the first six months after the start of treatment (349). Despite this evidence, a 2017 meta-analysis indicated that the prevalence of antipsychotics usage in the dementia population was approximately 30 % (350). In light of this data, the clinical decision to initiate treatment with atypical antipsychotics for NPS must only be done after careful assessment of the risk/benefit ratio.

Clear evidence supporting treatment of NPS with AChEIs is lacking (351). Data from previous research indicates modest effects on NPS, but due to the favorable cognitive profile, they are currently recommended as the first line of treatment (184). In patients with AD and DLB, where cholinergic dysfunction is paramount, treatment with AChEIs is recommended and may reduce the occurrence of NPS (352).

Unfortunately, a limited amount of viable options are available in the clinical setting. A 2018 meta-analysis including 36 RCTs demonstrated that only Risperidone, SSRIs as a class, and Dextromethorphan/quinidine (based on one study) were significantly better than placebo at reducing agitation as compared to placebo in patients with dementia (353). This clearly accentuates the need for

the development of novel treatment options with a better tolerability profile as well as improved efficacy, especially considering the magnitude of the disease burden attributed to agitation. Dextromethorphan/quinidine has been used to treat pseudobulbar affect and has demonstrated efficacy against agitation in dementia as compared to placebo with generally acceptable tolerability (354). Recently, a small placebo-controlled RCT evaluating the effect of the synthetic THC analog Nabilone showed a significant reduction in CMAI as compared to placebo, with limited adverse events, although increased sedation was observed in the Nabilone arm (192). Given the current scarcity of adequate treatment options, these and other hypothetical medications should be investigated with the utmost urgency, to at least increase the options for clinicians and patients when handled the difficult task of managing NPS in dementia.

5.1.3 Does treatment with AChEIs or atypical antipsychotics affect the CSF profile of core AD biomarkers?

Whether AChEIs or antipsychotic treatment could affect core AD pathology was one of our research questions at hand. Two previous autopsy studies conducted on LBD patients have demonstrated that antipsychotic therapy was associated with an increased amount of cortical NFT burden, whereas the use of AChEI was associated with a reduction in the amount of cortical Aβ depositions (355,356). Therefore, we hypothesized that similar alterations could be observed on the CSF profile of core AD biomarkers in our study population.

We observed a significant reduction of CSF Aβ1-42 by 8 % during longitudinal follow-up in the Risperidone treated patients, while no significant changes were seen in the Galantamine treated patients, nor in any of the other core AD biomarkers (*study IV*). Our data could not corroborate the previous study, indicating a relationship between antipsychotic medication and increased NFT burden, but instead suggested the possible role Risperidone has in the propagation of amyloid pathology as indicated by the reduced levels of Aβ1-42. No evidence supporting a pathology modifying role of AChEI could be observed. Given the proposed relationship between cognitive decline and the use of antipsychotics, this finding provides an interesting hypothesis for the causality of this phenomena. Multiple studies have indicated an association between an increased rate of cognitive decline and the use of antipsychotics in the dementia population (357–360), albeit two studies could not identify this relationship (361,362). A 2017 meta-analysis, only including RCTs, showed no significant effect of antipsychotics on cognition, albeit the duration of antipsychotic treatment was associated with cognitive decline (363).

This supports a previously postulated hypothesis that cognitive decline increases during long-term treatment periods with antipsychotics (185). Although the exact association between antipsychotics and deterioration of cognitive decline

remains to be determined, there is a significant amount of evidence supporting the detrimental effect on cognition. However, the mechanism by which this may be mediated is currently unknown. Speculatively, antipsychotics could affect core AD pathological mechanism by unknown pathways, as indicated by our study mediated via increased amyloid pathology. Albeit, the effects on cognition could also be the consequence of the sedative properties of the medications, mediated by anticholinergic or antihistaminergic effects. The antipsychotic Olanzapine has, for example, shown to have neurotoxic effects mediated by ROS, both in vivo and in vitro, causing mitochondrial damage when inhibiting cellular autophagy (364). Furthermore, the administration of both typical and atypical antipsychotics generate CSF findings indicative of neuronal death in AD patients (365). One could, therefore, hypothesize that normal autophagy could be disrupted due to the underlying neurodegenerative process in AD, thus potentially enabling antipsychotic neurotoxicity. Additionally, in vitro models of Clozapine and Haloperidol have demonstrated detrimental effects on neuronal viability, thought to be mediated by interference with the autophagic process, and multiple other neurotoxic mechanisms have been suggested (366,367). Studies of patients with schizophrenia have also demonstrated that long term use of both typical and atypical antipsychotics is associated with a reduction of grey matter volume, in the frontal and parietal cortex in a dose-dependent manner (368).

This raises further questions regarding the suitability of antipsychotic treatment in the dementia population. Albeit, it should be noted that a recent review of atypical antipsychotics indicates multiple different neuroprotective effects observed in preclinical studies involving both cell and animal models, although generalization of these results to humans in general and dementia patients, in particular, may be precarious (369). Of course, our observed decrease in Aβ1-42 amongst Risperidone treated patients could be attributed to progression of the underlying neurodegenerative process. This notion is however contradicted by earlier studies showing that CSF Aβ1-42 levels are stable during shorter follow-up, and also by the fact that no decrease was observed amongst Galantamine treated patients suggesting that Risperidone contributed to the observed decrease of Aβ1-42 (370,371).

AChEIs increase the amounts of Ach in the synaptic cleft, which mediates its effects by binding to different types of muscarinic and nicotinic receptors in CNS, both thought to be involved in AD pathology (372). In vitro studies and animal models have demonstrated that agonistic stimulation of the M1 muscarinic receptor reduces Aβ formation, thought to be mediated by stimulation of α-secretase, and thus shifting APP processing into the non-amyloidogenic pathway (373,374). Similarly, stimulation of the α7-nicotinic receptor generates less Aβ via upregulation of α-secretase (375). Treatment with the M1-receptor agonist Talsaclidine has also been shown to reduce levels of CSF Aβ1-42 in AD patients during follow-up,

interpreted by the authors as a positive finding, in contrast with the current interpretation of CSF Aβ1-42 levels (376). Medications targeting cholinergic receptors have been investigated in clinical trials but were discontinued due to lack of efficacy and adverse effects, although several compounds are currently in preclinical trials.

We could found not find any evidence that AChEI treatment affects AD pathology, as measured by CSF biomarkers, congruent with other research (371). However, agonistic stimulation of specific cholinergic receptors seems to have potential benefits on cognition, as well as theoretical disease-modifying pathways, thus generating interesting targets for future research (372). Speculatively, an obstacle in the development of efficient cholinergic agonists is the enormous complexity and wide spatial distribution of cholinergic receptors in both brain and body. This generates difficulties in creating compounds that act on the targets of relevance in specific brain regions, without interference with other systems likely to generate side effects observed in earlier studies.

5.1.4 Relationship between markers for synaptic/axonal injury and diagnosis, *APOE* and gender

In study IV, we investigated the differences in CSF levels of Ng, GAP-43 and NFL between grouping variables diagnosis, *APOE*-status and gender. Only CSF NFL differed between diagnostic subgroups after adjustment for covariates and cofactors, while *APOE*-ε4 homo- or heterozygotes and females had increased levels of CSF Ng. As discussed in study IV, previous research has indicated that alterations of both Ng and GAP-43 in CSF are specific for AD (206,227).

We observed higher median levels in CSF Ng and GAP-43 in AD patients compared to other groups, but this difference was not statistically significant, potentially due to insufficient sample size during subgroup analysis. Although, worth noting is that these studies did not conduct adjustment for age, gender and *APOE*-status as done in our study. Presence of *APOE*-ε4 has earlier been associated with increased CSF Ng, while one previous study has indicated that *APOE*-status only affects levels of Ng in Aβ- individuals (207,342). Thus, future research should include all these variables in order to determine their individual association to CSF levels of biomarkers for synaptic and axonal degeneration.

5.2 Limitations

Several conceptual limitations in these studies need to be considered. One major challenge in the field of NPS research, in general, is the correct quantification of the primary outcome variable, namely neuropsychiatric symptoms. Correct measurement and description of NPS constitutes a foundation for both research

and clinical practice in this area. Since all current assessment methods are based on patient or relative/caregiver recollection of behavior and events, there might be potential bias and inaccuracy embedded in this approach. Thus, it is always important to contemplate whether we have measured what we actually intended to quantify when using these types of data in research. Currently, rating scales such as the NPI are considered as the gold standard to asses NPS, collecting information from caregivers or relatives post hoc. Although this may be the best possible way to asses NPS burden, it seems fairly obvious that this method is prone to potential measurement errors due to, for example, recall bias (377). NPS also fluctuate over time, thus making the current point estimates potentially insufficient, an obstacle that can, to some extent, be amended using several longitudinal assessment points. Additionally, we assume that the measured NPS reflect a consequence of the underlying neurodegenerative disease. Albeit, the rating scales fail to provide context that could potentially explain the change in behavior. Furthermore, the patient's subjective experience of NPS is not assessed, and some NPS, such as compulsions, are not included. Overall, all these problems stem from the fact that complex human behavior is hard to objectively quantify, generating an inherited challenge in this field of research. Even using potential modern solutions, for example, video recordings, assessment of NPS and transfer of human behavior onto a numerical scale will always provide difficulties. A significant limitation is a lack of a placebo-group in the clinical trial, which reduced the ability to conclude on the clinical and CSF-based effects of the two medications. However, using a placebo for patients with clinically significant NPS is problematic from an ethical point of view.

Additionally, it is important to consider that measurement of CSF biomarkers provide a total crude output of the ongoing cerebral protein metabolism and transport into CSF, not taking to account possible regional differences that may be paramount for the pathophysiology. As previously described, regional pathology in specific neuronal circuits or monoaminergic pathways is more likely to be the culprit of NPS rather than general neurodegeneration. For example, this becomes evident in *study IV*, when attempting to provide an inference of associations between NPS and CSF GAP-43, due to the fact that GAP-43 in previous research has been shown to both increase and decrease in different brain regions during neurodegeneration (222). Thus, interpretation of synaptic dysfunction as measured by CSF biomarkers becomes somewhat speculative and may obscure regional pathology of relevance for the clinical phenotype, which is not observed in the total CSF output. Therefore, it is of utmost importance, to incorporate both CSF and imaging data in future research to improve the understanding of the spatial distribution of synaptic dysfunction in NPS.

Furthermore, some statistical aspects need to be considered. Overall, the included studies lack a sufficiently large sample size leading to reduced statistical power, in particular for the subgroup analyses. This increases the risk of type II errors and thus, potentially resulting in missing associations that actually exist. On the other hand, due to the exploratory setting of our studies, we performed multiple comparisons without using any correction, such as the Bonferroni method, thus increasing the risk of type I errors. Therefore, all found significant associations must be interpreted with caution given the possibility of incorrect rejection of the null hypothesis.

5.3. Summary and future considerations

In summary, research ranging from animal models to post-mortem neuropathological studies indicate specific NPS as a distinct neuropathological phenomenon. Most likely, associated with dysfunction of neuronal circuits and monoaminergic pathways involved in modulation of behavior, often preceding cognitive decline in the setting of neurodegenerative disorders. In AD, there seems to be evidence for the role of the core neurodegenerative process in the pathophysiology of NPS, which seems to be both symptom-specific whiles also sharing some common neuroanatomical pathways. Several AD-associated NPS display pathological alternations in overlapping neuroanatomical regions. In particular, the ACC has been associated with various NPS in imaging studies (299). Other brain regions often displaying pathological changes in the setting of NPS include frontal, temporal, parietal and subcortical regions. We have found support for the association of NPS burden with tau-associated pathology and synaptic dysfunction. In contrast, amyloid pathology seems to play a less pivotal role in the pathophysiology of NPS.

Future research should focus on the incorporation of currently existing research modalities, such as imaging and CSF biomarkers, into one comprehensive outlook in order to provide a complete interpretation of the associated neuropathology. For example, newly proposed imaging markers specific for synaptic dysfunction should be integrated, with CSF biomarker studies in order to better understand these complex relationships. Additionally, further research into blood biomarkers providing similar information to CSF biomarkers is needed, to find less invasive procedures for data collection, thus enabling larger-scale studies in the future. Finally, clinicians should think twice before prescribing antipsychotics for NPS in dementia, and preferably use it only as an exception, given the current scientific data. Even though causality between increased mortality and use of antipsychotics has not been established, the modest efficacy combined with the potential for harming the patient should be enough to carefully consider the cost-benefit/ratio.

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